



Efficacy and safety of remimazolam in bronchoscopic sedation: A meta-analysis

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Abstract

BACKGROUND

Remimazolam is a new benzodiazepine used for procedural sedation and general anesthesia. Several studies have used remimazolam for bendable bronchoscopy.

AIM

To assess the safety and efficacy of remimazolam for sedation in patients undergoing bendable bronchoscopy by performing a meta-analysis of randomized controlled trials (RCTs).

METHODS

We searched the EMBASE, PubMed, Cochrane Library, and Web of Science databases for RCTs on bendable bronchoscopic procedural sedation with remimazolam *vs* conventional sedatives (CS).

RESULTS

Five studies with 1080 cases were included. Remimazolam had the same sedation success rate compared with CS [relative risk (RR): 1.35, 95%CI: 0.60-3.05, $P = 0.474$, $I^2 = 99.6\%$]. However, remimazolam was associated with a lower incidence of hypotension (RR: 0.61; 95%CI: 0.40-0.95, $P = 0.027$; $I^2 = 65.1\%$) and a lower incidence of respiratory depression (RR: 0.50, 95%CI: 0.33-0.77, $P = 0.002$, $I^2 = 42.3\%$). A subgroup analysis showed a higher success rate of sedation with remimazolam than midazolam (RR: 2.45, 95%CI: 1.76-3.42, $P < 0.001$). Compared with propofol, the incidence of hypotension (RR: 0.45, 95%CI: 0.32-0.64, $P < 0.001$, $I^2 = 0.0\%$), respiratory depression (RR: 0.48, 95%CI: 0.30-0.76, $P = 0.002$, $I^2 = 78.4\%$), hypoxemia (RR: 0.36, 95%CI: 0.15-0.87, $P = 0.023$), and injection pain (RR: 0.04, 95%CI: 0.01-0.28, $P = 0.001$) were lower.

CONCLUSION

Remimazolam is safe and effective during bronchoscopy. The sedation success rate was similar to that in the CS group. However, remimazolam has a higher safety profile, with fewer inhibitory effects on respiration and circulation.

Key Words: Remimazolam; Bronchoscopy; Procedural sedation; Meta-analysis

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Core Tip: We searched the databases of EMBASE, PubMed, Cochrane Library, and the Web of Science for randomized controlled trials of bendable bronchoscopic procedural sedation with remimazolam vs conventional sedatives (CS) from the time the database was created until August 2023. STATA 15.1 software was applied to data analyses. Five studies with 1080 cases were included. We finally came to the conclusion: Remimazolam is safe and effective for cases with bronchoscopy. Its sedation success rate is similar to CS. However, remimazolam has a higher safety profile with less inhibitory effects on respiration and circulation.

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INTRODUCTION

Bronchoscopy is an endoscopic tool for the diagnosis and treatment of respiratory disease, and plays a key role in the diagnosis and therapy of lung diseases[1]. However, bendable bronchoscopy is an invasive procedure, and patients often experience pain and anxiety as well as serious complications including respiratory depression, cardiac arrhythmias, and cerebrovascular accidents[2]. According to the American Thoracic Society, anesthesia is recommended for all patients undergoing bronchoscopic consultations in the absence of contraindications[3]. Procedural sedation involves the use of sedative drugs and analgesics in addition to routine consultation, which eliminates fear, improves comfort, increases tolerance, and reduces procedural complications while shortening the duration of the procedure[4].

Currently, conventional sedatives (CS) propofol, midazolam, and dexmedetomidine are widely used in painless bendable bronchoscopy practice. Propofol has a rapid onset of action and a short recovery time; however, it causes significant injection site pain, strong respiratory and circulatory depression, and has no antagonist[5]. Midazolam is antagonized by flumazenil. However, the prolonged postoperative sedation affects the time to discharge. Dexmedetomidine is a selective α_2 -adrenergic receptor agonist with sedative properties[6]. One study reported that dexmedetomidine has a low likelihood of causing respiratory depression but a long recovery time[7].

Remimazolam is a new and effective benzodiazepine whose metabolites are not pharmacologically active, resulting in a faster recovery of cognitive function[8]. Owing to its unique pharmacological properties, remimazolam has been widely used in endoscopy, particularly in gastroenteroscopy[9]. In recent years, with the development of painless diagnostic techniques, the use of remimazolam for bendable bronchoscopy has received much attention. However, there has been no relevant systematic review. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) on remimazolam for bronchoscopy to compare its safety with that of CS.

MATERIALS AND METHODS

Search strategy

We searched the EMBASE, PubMed, Cochrane Library, and Web of Science databases from the origin to August 2023. The search terms include "Remimazolam" or "CNS 7056," search scope was "Title and Abstract." The search was limited to human studies in English. Relevant studies were independently obtained by two investigators.

Our inclusion criteria were as follows: (1) RCT study design; (2) patients underwent bendable bronchoscopy; (3) the interventional treatment was either Remimazolam or CS; (4) papers published from establishment to August 1, 2023; and (5) studies that were not in Chinese or English, duplicated, or had incomplete data were excluded.

Data extraction

The data were independently analyzed to extract relevant information: (1) Authors; (2) publication time; (3) country of publication; (4) type of study design; (5) American Society of Anesthesiologists classification (ASA classification); (6) number of participants in each study; (7) age range; (8) sex composition; and (9) specific interventions received by the participants, including the name of the medication, dosage, and dosing program. Disagreements in the extracted data

Table 1 The basic characteristics of included studies

| Ref. | Country | Study design | ASA status | Number of patients | Age | Gender (M/F) | Remimazolam | Control |
|--------------------------------|---------|--------------|------------|--------------------|-------|--------------|--|---|
| Gao <i>et al</i> [13], 2023 | China | RCT | I-III | 60 | 18-70 | 39/21 | Initial dose: 6 mg/kg/h; Maintenance dose: 0.6-2 mg/kg/h | Propofol: Initial dose: 2 mg/kg; Maintenance dose: 4-6 mg/kg/h |
| Zhang <i>et al</i> [14], 2023 | China | RCT | I-III | 192 | 18-64 | 92/100 | Initial dose: 0.2 mg/kg; Top-up dose: 0.05 mg/kg | Propofol: Initial dose: 1.5 mg/kg; Top-up dose: 0.5-1.0 mg/kg |
| Zhou <i>et al</i> [15], 2022 | China | RCT | I-III | 310 | 18-75 | 154/156 | Initial dose: 0.2 mg/kg; Top-up dose: 0.1 mg/kg | Propofol: Initial dose: 2 mg/kg; Top-up dose: 0.75 mg/kg |
| Pastis <i>et al</i> [16], 2019 | USA | RCT | I-III | 372 | 50-74 | 174/198 | Initial dose: 5 mg; Top-up dose: 2.5 mg | Midazolam: Initial dose: 1-1.75 mg; Top-up dose: 0.5-1 mg |
| Chen <i>et al</i> [17], 2022 | China | RCT | I-III | 146 | 45-65 | 108/38 | Initial dose: 12 mg/kg/h; Maintenance dose: 1-2 mg/kg/h | Dexmedetomidine: Initial dose: 0.5 µg/kg; Maintenance dose: 0.2-0.7 µg/kg/h |

ASA: American Society of Anesthesiologists.

Table 2 Number of successful sedation in bronchoscopy

| Ref. | Study design | Number of patients in each group | | Number of successful sedation | |
|--------------------------------|--------------|----------------------------------|---------------------|-------------------------------|---------------------|
| | | Remimazolam | Control | Remimazolam | Control |
| Zhou <i>et al</i> [15], 2022 | RCT | 155 | Propofol: 155 | 154 | Propofol: 154 |
| Pastis <i>et al</i> [16], 2019 | RCT | 310 | Midazolam: 73 | 250 | Midazolam: 24 |
| Chen <i>et al</i> [17], 2022 | RCT | 73 | Dexmedetomidine: 73 | 69 | Dexmedetomidine: 67 |

RCT: Randomized controlled trial.

were recorded and discussed with a 3rd researcher until a consensus was reached.

Quality assessment

Two researchers evaluated the quality of the research papers. The Cochrane tool[10] was applied to calculate the risk of bias. Under the study conditions, items related to high or unclear bias risk were regarded as high risk[11]. Disagreements in quality evaluation were documented and discussed with a third researcher until a consensus was reached.

Statistical analysis

All statistical analyses were conducted using STATA15.1 (Stata Statistical Software: Release 18. College Station, TX: StataCorp). *I*² and *Q* tests were used to test the heterogeneity between studies. If heterogeneity between studies existed (*I*² ≤ 50% and *P* > 0.10), the data was analyzed *via* a fixed-effects model; otherwise, a random-effects model was used[12]. Subgroup analyses were conducted to compare the effects of propofol, midazolam, and dexmedetomidine; *P* < 0.05 was regarded as statistically significant.

RESULTS

Study selection

As shown in Figure 1, 40 studies were identified after a systematic literature search. After removing 20 duplicate studies, the 20 remaining studies were screened. Eight inappropriate studies were eliminated by screening titles and abstracts. Therefore, 12 articles were left for full-text reading. After careful reading of the full text, seven studies were excluded based on the inclusion and exclusion criteria. Finally, five studies were included.

Studies and participants' characteristics

Table 1 shows all the studies included, all five studies[13-17] were RCTs, four[13-15,17] were from China, and one[16] was from the United States. The five studies[13-17] were classified as ASA classes I-III. In studies published between 2018 and 2023, 1080 patients aged from 18 to 75 years, and 52.50% male underwent bendable bronchoscopy; 657 patients were sedated with remimazolam and 423 patients were sedated with CS, of which 281 were sedated with propofol[13-15], 69 with midazolam[16], and 73 with dexmedetomidine[17].

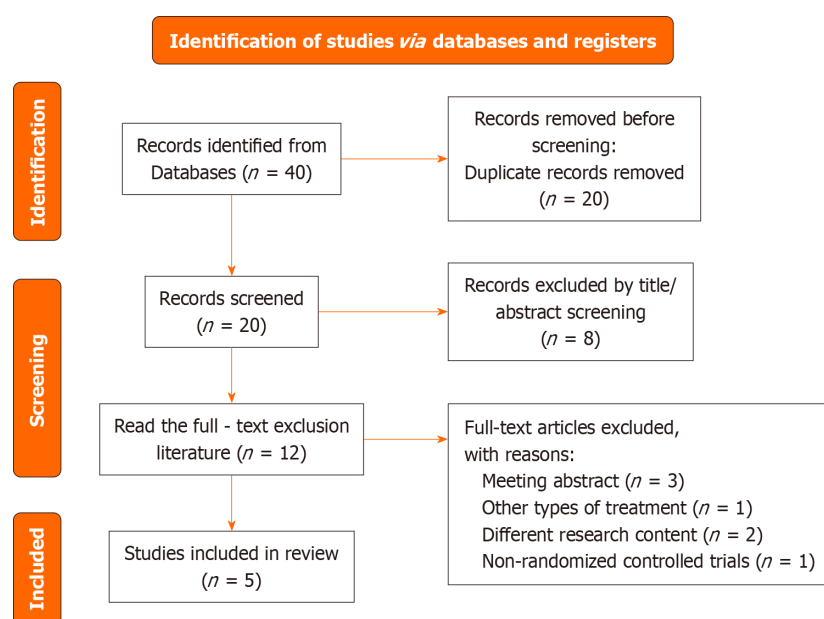


Figure 1 Flow diagram of study searching and selection process.

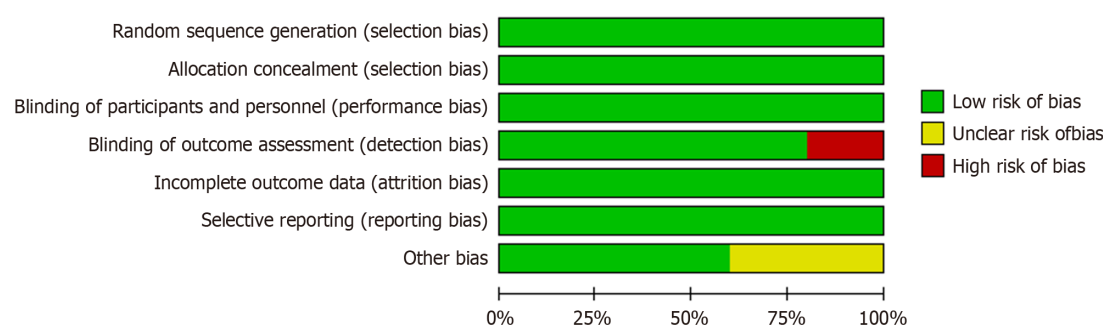


Figure 2 The risk of bias graph of included studies. The five studies showed a low bias risk for they assessed randomized sequence generation (100%), blinding of participants (100%), blinding of outcome (80%), selective reporting (100%), and others (60%).

The same standard was applied to evaluate sedation in 3 studies[15-17]. These studies divided patients into two groups according to the type of sedation used. The percentages of successfully sedated patients were 473/538 using remimazolam and 245/301 in the CS group (propofol 154/155, midazolam 24/73, and dexmedetomidine 67/73) (Table 2). The frequencies of intraoperative adverse events and complications, including hypotension, respiratory depression, and hypoxemia, are shown in Table 3.

Risk of bias assessment

The Cochrane method was used to calculate the risk of bias in the RCTs, as shown in Figures 2 and 3. Five studies showed a low risk of bias for randomized sequence generation (100%), blinding of participants (100%), blinding of outcomes (80%), selective reporting (100%), and others (60%). Three of these exhibited high quality according to the assessment results (Figures 2 and 3).

Results of the meta-analysis

The sedative efficiency: Three studies[15-17] reported the success rates of sedation with remimazolam and CS, involving 1032 cases (research group, $n = 538$; CS group, $n = 301$). The heterogeneity test results, $I^2 = 99.6\%$ and $P < 0.001$ in the Q-test, indicate statistically significant heterogeneity among different studies. Therefore, a random-effects model was used for subsequent tests. As shown in Figure 4, the relative risk (RR) value of the 3 studies pooled was 1.35, (95%CI: 0.60-3.05), $P = 0.474$, suggesting that the success rate of remimazolam for bronchoscopic sedation was similar to that of CS.

As shown in Figure 5, subgroup analysis showed that the success rate of remimazolam sedation was similar to that of propofol (RR: 1, $P = 1.000$), remimazolam sedation was more successful than midazolam sedation (RR: 2.45, $P \leq 0.001$), and remimazolam and dexmedetomidine had similar sedation success rates (RR: 1.03, $P = 0.513$).

The incidence of adverse events: As shown in Table 4, there was a significant difference in the incidence of hypotension and respiratory depression between the remimazolam and CS groups (hypotension: RR = 0.61, $I^2 = 65.1\%$, $P = 0.027$;

Table 3 The number of patients with adverse events during bronchoscopy

| Ref. | Patients in each group (n) | | Hypotension (n) | | Hypertension (n) | | Respiratory depression (n) | | Hypoxemia (n) | | Bradycardia (n) | | Tachycardia (n) | | Injection pain (n) | |
|--------------------------------|----------------------------|----------------------|-----------------|---------------------|------------------|---------------------|----------------------------|---------------------|---------------|---------------------|-----------------|---------------------|-----------------|---------------|--------------------|---------------|
| | Remimazo lam | Control | Remimazo lam | Control | Remimazo lam | Control | Remimazo lam | Control | Remimazo lam | Control | Remimazo lam | Control | Remimazo lam | Control | Remimazo lam | Control |
| Gao <i>et al</i> [13], 2023 | 30 | Propofol: 30 | 11 | Propofol: 22 | 1 | Propofol: 2 | NA | NA | 1 | Propofol: 2 | 2 | Propofol: 5 | 6 | Propofol: 9 | NA | NA |
| Zhang <i>et al</i> [14], 2023 | 96 | Propofol: 96 | 1 | Propofol: 8 | NA | NA | 13 | Propofol: 38 | NA | NA | 0 | Propofol: 22 | NA | NA | NA | NA |
| Zhou <i>et al</i> [15], 2022 | 155 | Propofol: 155 | 22 | Propofol: 49 | 13 | Propofol: 5 | 9 | Propofol: 8 | 13 | Propofol: 5 | NA | NA | NA | NA | 1 | Propofol: 26 |
| Pastis <i>et al</i> [16], 2019 | 303 | Midazolam : 69 | 127 | Midazolam : 34 | 186 | Midazolam : 41 | 7 | Midazolam : 3 | 186 | Midazolam : 41 | 13 | Midazolam : 3 | 4 | Midazolam : 0 | 2 | Midazolam : 0 |
| Chen <i>et al</i> [17], 2022 | 73 | Dexmedeto midine: 73 | 9 | Dexmedeto midine: 8 | 2 | Dexmedeto midine: 3 | 2 | Dexmedeto midine: 2 | 2 | Dexmedeto midine: 3 | 3 | Dexmedeto midine: 2 | NA | NA | NA | NA |

respiratory depression: RR = 0.50, $I^2 = 42.3\%$, $P = 0.002$). The incidence of hypertension, hypoxemia, bradycardia, tachycardia, and injection pain was similar between the two groups.

As shown in Table 5, subgroup analyses revealed obvious differences between the two groups in the incidence of hypotension, respiratory depression, hypoxemia, and injection pain (hypotension: RR = 0.42, $I^2 = 0.0\%$, $P < 0.001$; respiratory depression: RR = 0.48, $I^2 = 78.4\%$, $P = 0.002$; hypoxemia: RR = 0.4, $I^2 = 0.0\%$, $P < 0.001$; and injection pain: RR = 0.04, $I^2 = 0.0\%$, $P < 0.001$). There was no obvious heterogeneity in the incidence of hypertension, bradycardia, or tachycardia among groups. The pooled results suggested that there was no significant difference in the incidence of hypotension, hypertension, respiratory depression, hypoxemia, bradycardia, tachycardia, or injection pain between remimazolam and midazolam. Similarly, there was no heterogeneity in the incidence of hypotension, respiratory depression, hypoxemia, tachycardia, or injection pain between the two groups.

DISCUSSION

This study aimed to explore the efficacy and safety of remimazolam during bronchoscopy. Based on these results, remimazolam had a sedation success rate similar to that of CS. However, remimazolam was associated with a lower risk of hypotension and respiratory depression than was CS. It can be concluded that remimazolam for bronchoscopy provides satisfactory sedation and a favorable safety profile. We compared the efficacy and safety of that with CS (propofol, midazolam, and dexmedetomidine) in bronchoscopic sedation, analyzing a total of 5 studies on the application of remimazolam for bronchoscopy. Of these, three papers compared remimazolam *vs* propofol, one used midazolam, and one used dexmedetomidine. Due to the heterogeneity among the three sedative drugs, this study conducted a meta-analysis and found that remimazolam showed a higher success rate of sedation than midazolam. Compared with

Table 4 Pooled results on the incidence of adverse events for remimazolam versus conventional sedatives

| Control | Complications | Relative risk | 95%CI | P value (%) | P value for effect |
|------------------------|------------------------|---------------|--------------|-------------|--------------------|
| Conventional sedatives | Hypotension | 0.61 | (0.40, 0.95) | 65.1 | 0.027 |
| | Hypertension | 1.11 | (0.89, 1.38) | 23.5 | 0.359 |
| | Respiratory depression | 0.50 | (0.33, 0.77) | 42.3 | 0.002 |
| | Hypoxemia | 0.74 | (0.37, 1.47) | 59.7 | 0.387 |
| | Bradycardia | 0.72 | (0.33, 1.56) | 0.0 | 0.403 |
| | Tachycardia | 0.78 | (0.33, 1.85) | 0.0 | 0.576 |
| | Injection pain | 0.17 | (0.01, 5.30) | 72.3 | 0.316 |

Table 5 Pooled results of subgroup analyses of adverse event rates for remimazolam vs propofol, midazolam, and dexmedetomidine

| Control | Complications | Relative risk | 95%CI | P value (%) | P value for effect |
|-----------------|------------------------|---------------|---------------|-------------|--------------------|
| Propofol | Hypotension | 0.45 | (0.32, 0.64) | 0.0 | 0.000 |
| | Hypertension | 2.00 | (0.82, 4.85) | 37.6 | 0.125 |
| | Respiratory depression | 0.48 | (0.30, 0.76) | 78.4 | 0.002 |
| | Hypoxemia | 0.36 | (0.15, 0.87) | - | 0.023 |
| | Bradycardia | 0.33 | (0.08, 1.33) | 0.0 | 0.119 |
| | Tachycardia | 0.67 | (0.27, 1.64) | - | 0.378 |
| | Injection pain | 0.04 | (0.01, 0.28) | - | 0.001 |
| Midazolam | Hypotension | 0.85 | (0.65, 1.12) | - | 0.247 |
| | Hypertension | 1.03 | (0.83, 1.28) | - | 0.766 |
| | Respiratory depression | 0.53 | (0.14, 2.00) | - | 0.350 |
| | Hypoxemia | 1.16 | (0.68, 1.97) | - | 0.595 |
| | Bradycardia | 0.99 | (0.29, 3.37) | - | 0.983 |
| | Tachycardia | 2.07 | (0.11, 38.05) | - | 0.624 |
| | Injection pain | 1.15 | (0.06, 23.72) | - | 0.927 |
| Dexmedetomidine | Hypotension | 0.61 | (0.40, 0.95) | - | 0.797 |
| | Hypertension | 0.67 | (0.11, 3.87) | - | 0.652 |
| | Respiratory depression | 1.00 | (0.14, 6.91) | - | 1.000 |
| | Hypoxemia | 0.80 | (0.33, 1.91) | - | 0.616 |
| | Bradycardia | 1.50 | (0.26, 8.71) | - | 0.652 |

propofol, remimazolam has a lower risk of hypotension, respiratory depression, and injection pain.

Remimazolam is a novel benzodiazepine analog[18]. It can be quickly metabolized *in vivo* by esterases independent of renal metabolism, and its metabolites are inactive[19]. The effects of this drug can be reversed by flumazenil, with a rapid onset of action and safe sedation[20]. In addition, the use of remimazolam reduces patient healthcare costs compared with midazolam during bronchoscopy[21]. Therefore, it is a promising drug for bronchoscopic diagnosis and therapy[22]. The number of endoscopic procedures is increasing, and anesthesia is beneficial for endoscopic procedures[9,23]. Anesthetic drug selection for bronchoscopic surgery should improve the safety of the procedure without compromising the success rate[24,25]. This meta-analysis showed that remimazolam reduced intraoperative adverse events and complications while maintaining the sedation success rate.

When writing this article, we identified two similar systematic reviews and meta-analyses[26,27] that compared the reliability and safety of other sedatives in endoscopy, however, we incorporated a wider range of adverse events and complications which included hypotension, hypertension, respiratory depression, hypoxemia, bradycardia, tachycardia, and injection pain, to evaluate the safety of remimazolam more comprehensively. Our study showed that remimazolam exhibited the same success rate as CS for bronchoscopy, which is in contrast to existing studies[27] that stated that remimazolam had a higher procedural success rate than CS. This may be related to the diverse types of endoscopies included in that report, including upper gastrointestinal endoscopy, colonoscopy, hysteroscopy, and bronchoscopy,

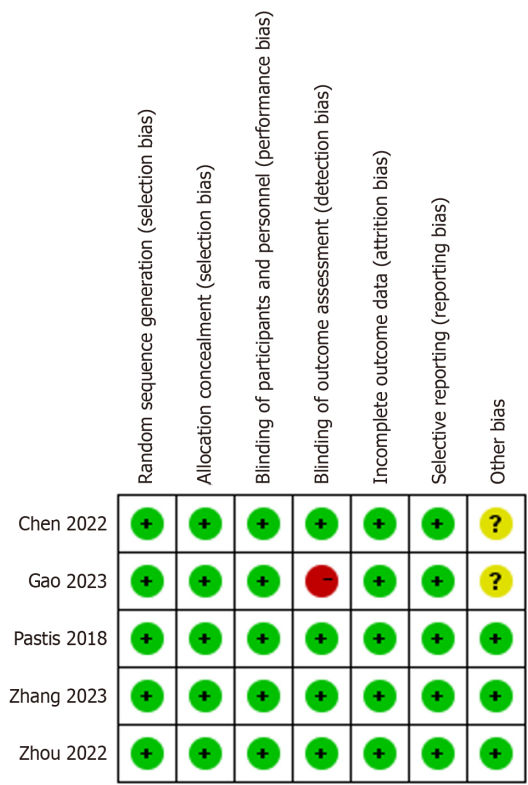


Figure 3 The risk of bias summary of included studies. Three of the five studies exhibit high quality according to the assessment result.

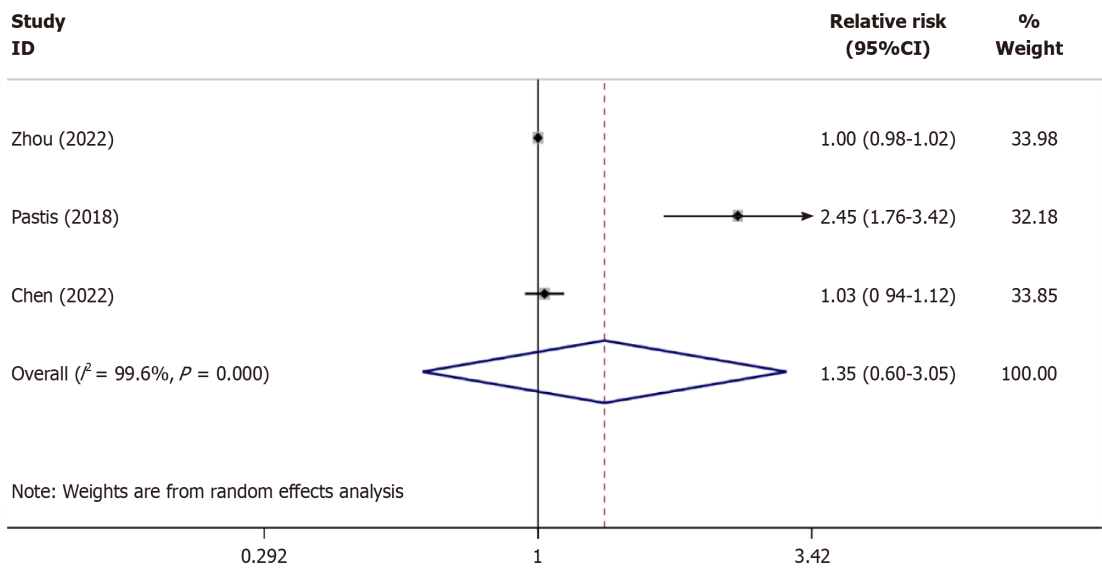


Figure 4 Comparison of the sedation success of remimazolam with conventional sedatives. A total of three studies investigated the sedation success of remimazolam vs conventional sedatives, and pooled analyses showed equal sedation success.

whereas only 1 bronchoscopy was included which was clinically heterogeneous. Furthermore, bronchoscopy is generally more stimulating than gastrointestinal endoscopy and hysteroscopy and requires deeper intraoperative sedation[28]. Further studies are warranted to investigate the success of remimazolam *vs* other sedatives at different sedation depths. The occurrence of hypotension and injection pain was lower in patients for whom remimazolam was used for sedation compared with propofol, which is consistent with two previous reports[26,29]. This suggests that remimazolam offers significant advantages in terms of respiration, circulation, and pain during injection.

Our study is the first to explore the efficacy of remimazolam *vs* CS in bronchoscopic procedures using subgroup analysis, providing evidence for the selection of bronchoscopic sedation drugs that remimazolam is safe and effective for bronchoscopic sedation. In clinical practice, patients undergoing bronchoscopy are predominantly elderly and chronically ill[30], and remimazolam facilitates intraoperative safety and postoperative recovery by significantly reducing respiratory and circulatory depression compared to CS. However, our study has some limitations. First, the definitions of different

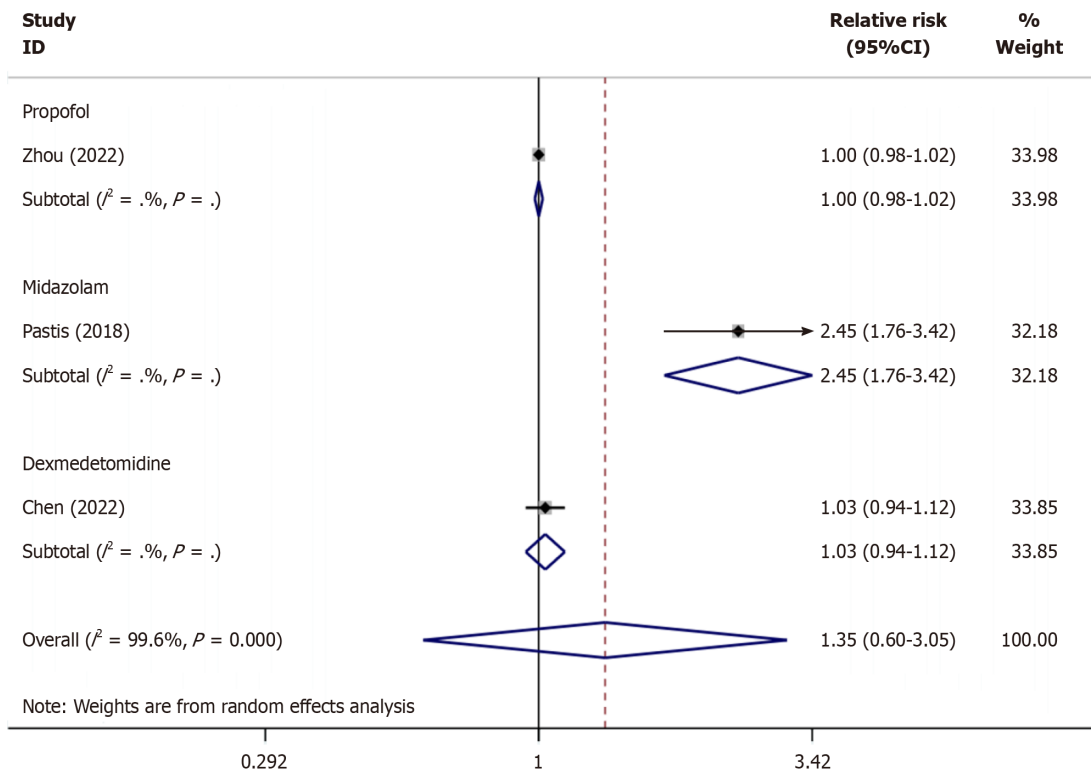


Figure 5 Subgroup analysis of the sedation success of remimazolam compared with propofol, midazolam, and dexmedetomidine. The results showed that there was no significant difference in sedation success between remimazolam and propofol, remimazolam sedation success was higher than midazolam, and there was no significant difference in sedation success between remimazolam and dexmedetomidine.

types of surgical operations, sedation drugs, sedation doses, and outcome metrics varied, which may have influenced the results. Second, most of the patients in the included studies were from China, and there may be racial differences between the populations. Third, different types and uses of opioids in the included studies may have affected the results. Fourth, only a few studies were included because there is limited research on anesthesia during bronchoscopic surgery. There were fewer within-group studies in which we performed subgroup analyses. The reliability of the outcome metrics in a single study was examined, and more studies are needed for future analyses.

CONCLUSION

Remimazolam is safe and effective during bronchoscopy. The sedation success rate was similar to that of the traditional sedatives (propofol, midazolam, and dexmedetomidine). However, it exhibits a weaker inhibitory effect on respiration. Some scholars have reported the sedation efficacy and incidence of adverse events of remimazolam during bronchoscopy, and RCTs with more samples are needed to validate our findings.

ARTICLE HIGHLIGHTS

Research background

Remimazolam is a new ultra-short-acting benzodiazepine sedative that is currently used for procedural sedation and general anesthesia. Several studies have used remimazolam for bendable bronchoscopes.

Research motivation

This is the first systematic review on the safety and efficacy of remimazolam during bronchoscopy.

Research objectives

This study aimed to assess the safety and efficacy of remimazolam for the sedation of patients undergoing bendable bronchoscopy.

Research methods

We searched databases of EMBASE, PubMed, Cochrane Library, and the Web of Science, from the original to August

2023. The search terms include "Remimazolam" or "CNS 7056", search scope was "Title and Abstract". The search was limited to human studies and literature in English.

Research results

This meta-analysis included five studies. The sedation success rate of remimazolam was similar to that of conventional sedatives (CS). However, remimazolam is associated with a lower incidence of hypotension and respiratory depression. The subgroup analysis showed a higher success rate for sedation with remimazolam than with midazolam. The incidences of hypotension, respiratory depression, hypoxemia, and injection pain were lower with remimazolam than with propofol.

Research conclusions

Remimazolam is safe and effective for bronchoscopic sedation. The success rate was similar to that of CS. However, remimazolam has a higher safety profile, with fewer inhibitory effects on respiration and circulation.

Research perspectives

Endoscopic surgery outside the operating room is currently increasing, and anesthesia provides strong support for the development of endoscopic surgery. The use of remimazolam can fulfill sedation requirements during bronchoscopic procedures while reducing the incidence of intraoperative adverse events and complications.

FOOTNOTES

Author contributions: Zhou Y and Liu JT conducted the systematic review and data collection and proposed an explanation that played an important role in the writing of the paper; Zhao C and Tang YX evaluated and verified the manuscript; Tang YX analyzed the data and reviewed the article; Liu JT developed the concept of reviewing papers and supervised, critically evaluated, and confirmed the manuscript; This article was written and approved by all authors.

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