

# Safety and Efficacy of the Moderate Sedation During Flexible Bronchoscopic Procedure

## *A Systematic Review and Meta-Analysis of Randomized Controlled Trials*

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**Abstract:** Moderate sedatives have been increasingly used to improve patient comfort during flexible bronchoscopy (FB). However, routine use of moderate sedation during FB is controversial because its efficacy and safety are not well established.

This study aims to evaluate the efficacy and safety of moderate sedation during FB.

A search was made of Medline, EMBASE, and the Cochrane Library to May 2014.

Randomized controlled trials (RCTs) and quasi-RCTs were included.

The main analysis was designed to examine the efficacy of moderate sedation during FB in sedation than no-sedation.

The willingness to repeat FB was significantly more in sedation than no-sedation (odds ratio [OR] 2.30; 95% confidence interval [CI] 1.11–4.73;  $P = 0.02$ ;  $I^2 = 22.5$ ). The duration of FB was shorter in sedation group than no-sedation group (standardized mean difference [SMD]  $-0.21$ ; 95% CI  $-0.38$  to  $-0.03$ ;  $P = 0.02$ ;  $I^2 = 78.3\%$ ). Event of hypoxia was not significantly different between sedation and no-sedation groups (OR 0.86; 95% CI 0.42–1.73;  $P = 0.67$ ;  $I^2 = 0\%$ ). The SpO<sub>2</sub> during procedure was not different between sedation and no-sedation groups (SMD  $-0.14$ ; 95% CI  $-0.37$  to  $0.08$ ;  $P = 0.21$ ;  $I^2 = 49.9\%$ ). However, in subgroup analysis without supplemental oxygen, the SpO<sub>2</sub> was significantly lower in sedation than no-sedation group (SMD  $-0.45$ ; 95% CI  $-0.78$  to  $-0.11$ ;  $P = 0.01$ ;  $I^2 = 0.0\%$ ).

According to this meta-analysis, moderate sedation in FB would be useful in patients who will require repeated bronchoscopies as well as safe in respiratory depression. To our knowledge, although the various sedative drugs are already used in the real field, this analysis was the first attempt to quantify objective results. We anticipate more definite and studies designed to elucidate standardized outcomes for moderate sedation in FB.

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**Abbreviations:** CI = confidence interval, FB = flexible bronchoscopy, OR = odds ratio, RCTs = randomized controlled trials, SMD = standardized mean, VAS = visual analogue scale.

## INTRODUCTION

Flexible bronchoscopy (FB) is commonly used for the diagnosis and management of a variety of respiratory diseases. However, patient who undergoes FB frequently suffers pain, cough, sensation of asphyxiation, and unpleasant memories. Therefore, many bronchoscopists and patients prefer to use sedation during the procedure<sup>1–3</sup> for the purpose of facilitated performance and reduced discomfort, apprehension, and unpleasant memories.<sup>4,5</sup>

It was generally performed in a procedure room using moderate sedation (previously known as conscious sedation). Under moderate sedation patients have purposeful response to verbal or tactile stimuli and do not require an airway intervention as adequate spontaneous breathing is maintained. However, routine use of these sedative drugs is controversial because its efficacy and safety are not well established. FB under moderate sedation may have serious complications including respiratory depression such as hypoxia or hypercapnia and cardiovascular instability.<sup>6</sup> In addition, protocols without concrete evidence for sedation during FB vary by physician, institution, and geographic location.

There have been various trials of sedation during FB, but to date, there has not been any systematic review with meta-analysis for moderate sedation during FB in a procedure room. In this study, we performed a systematic review and comprehensive meta-analysis of randomized controlled trials (RCTs) to compare the safety (desaturation during procedure) and efficacy (willing to next FB) of moderate sedation during FB.

## MATERIALS AND METHODS

The methods for including articles and analysis and reporting the results of meta-analyses are specified a priori in a protocol developed based on recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>7</sup> An ethics review of systematic reviews and meta-analysis studies, such as this study, was not required per our institutional Health Research Ethics Board.

## Literature Search Strategy

We searched MEDLINE (1948 to May 2014), EMBASE (1980 to May 2014), and the Cochrane Register of Controlled Trials (CENTRAL) of the Cochrane Library (Issue 4, 2014) using the search filter in the Ovid database (SIGN; <http://www.sign.ac.uk>). The search terms were “bronchoscopy,” “fiber optic technology,” “conscious sedation,” “anesthesia,” “premedication,” “hypnotic sedative agent,” “midazolam,”

“diazepam,” “benzodiazepine,” “fentanyl,” “alfentanyl,” “remifentanyl,” “opioid\*,” “propofol,” “diisoprofol,” “diprivan,” “disoprivan,” “disoprofol,” “rapinovel,” “recofol,” “diisopropylphenol,” “dexmedetomidine,” “Meperidine,” “Thiopentone,” “Diphenhydramine,” “Droperidol,” and “promethazine.” We also reviewed the bibliographies of relevant review papers to identify additional publications. Finally, we searched an international database (<http://www.clinicaltrials.gov>) for trial registrations to identify ongoing or recently completed trials. The search was performed without restriction with respect to language or year of publication. The latest date for updating the search was May 29, 2014.

### Selection Criteria for Studies

Two authors (JP and EYC) independently evaluated the eligibility of all studies to determine whether they met all of the inclusion criteria. Disagreements between the 2 authors were resolved by discussion and consensus. The eligibility criteria included all of the following: study design—RCTs that compared outcomes of moderate sedation between at least 2 active study arms or 1 active study arm and 1 placebo or no-sedation arm were included. Studies comparing different modes of administration of the same agent were excluded unless there was another comparator group. Population—unselected adults undergoing FB. We excluded studies of rigid bronchoscopy or bronchoscopy with endobronchial ultrasound or brachytherapy. Intervention—moderate sedation compared with no-sedation. Outcomes—the primary outcome was the patient’s willingness to undergo repeat examination. Secondary outcomes were efficiency of the procedure such as procedure time, visual analogue scale (VAS) for pain and cough, pulse oxygen saturation during FB, the event of severe hypoxia, heart rate, and blood pressure. Severe hypoxia defined as  $SpO_2 \leq 85\%$  or  $< 90\%$  according to each research. Patients undergoing invasive bronchoscopy/rigid bronchoscopy, endobronchial ultrasound bronchoscopy, brachytherapy, thermoplasty, etc., were excluded. Studies that did not provide quantitative data for the meta-analysis were excluded.

### Data Extraction and Quality Assessment

The 2 authors (JP and EYC) independently extracted data using a standardized form developed in advance. Only published data were used. The 2 authors assessed the quality of the included trials, evaluating the risk of bias in the table for sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias as recommended in the Cochrane Handbook of Systematic Reviews 5.1. The authors compared their evaluations and reassessed the studies together as necessary. Disagreement was solved by discussion and consensus between the authors.

### Statistical Analysis

Clinical outcomes in our analysis can be categorized as binary data or continuous data. The odds ratio (OR) was used as the summary effect for the binary outcome, and the standardized mean difference (SMD) was used as the summary effect of the continuous outcome. The SMDs and their respective 95% confidence intervals (CI) were calculated based on the fixed-effect model using the inverse variance method.<sup>8</sup> The data also were inspected to test whether an analysis with a random-effects model using the method of DerSimonian & Laird (with the

estimate of heterogeneity being taken from the inverse-variance fixed-effect model) could identify a relevant “interaction.” A test for interaction (heterogeneity or trend) aims to determine whether or not there is evidence of difference in effect sizes between subgroups. The weights as a percentage of the overall total were applied to find separately the interaction(s) within each subgroup. Statistical heterogeneity between trials was analyzed using Cochran Q statistic ( $P < 0.1$  used for statistical significance) and by the  $I^2$  statistic. A test of whether the summary effect measure is equal to the null is given, as well as a test for heterogeneity, that is, whether the true effect in all studies is the same. Heterogeneity is also quantified using the  $I^2$  statistic.<sup>9</sup>  $I^2$  values  $> 50\%$  were considered substantial evidence of statistical heterogeneity. Meta-analyses were conducted using the “metan” command<sup>8</sup> in Stata SE 13.1 for Mac (StataCorp, TX). The methodological quality of the trials selected was assessed using the criteria described in the Cochrane Handbook.<sup>10</sup> We prespecified subgroup analysis according to the supplemental oxygen or use atropine for premedication. Oxygen saturation is associated with supplemental oxygen during procedure. Atropine was used before procedure to limit excessive salivary secretion and reduce vagal reflex influence on the heart. Atropine also has sedative effects and enhances sedative effects of benzodiazepine or opioids administered at the same time.

## RESULTS

### Search Results and Trial Characteristics

The process of identifying eligible studies is shown in Figure 1. We identified 1364 citations from electronic databases and selected potentially relevant articles for full text assessment. Articles in this group were excluded from the meta-analysis for the following reasons: no RCTs (2), duplication (6), other language (6), procedures were rigid bronchoscopy or intervention with FB (11), trials were conducted with no sedative drug ( $n = 90$ ), and comparisons between sedatives (19). Finally, we included 9 studies in the analysis.<sup>11–19</sup>

The characteristics of the included studies are shown in Table 1. All of them were prospective RCTs. The benzodiazepine (5 midazolam, 2 diazepam, 1 lorazepam) or propofol were used for moderate sedation during FB (Table 1). Four of 9 studies supplied oxygen during FB, routinely. Five of 9 studies used the premedication with atropine. Except one study, questionnaires for comfort to patients or bronchoscopist were performed within 3 hours at termination of procedure. There was not clarified who administered the sedation during procedure in all studies. The age in enrolled studies was not different among groups (SMD  $-0.12$ ; 95% CI  $-0.3$  to  $0.05$ ;  $I^2 = 64\%$ ;  $P = 0.18$ ). Two studies had a significantly lower age in sedation group than in no-sedation group. The ratio of male and female was not different among groups (OR  $1.12$ ; 95% CI  $0.8$ – $1.59$ ;  $I^2 = 0\%$ ;  $P = 0.5$ ). Each study evaluated different outcome values of sedative agent such as “willing to repeat BFS,” “VAS for procedure tolerance, cough and pain,” and “unpleasant feeling” (Table 2).

The assessments of risk of bias item for each included RCT are performed by the authors and shown in Table 3. The low risk was 22.2% of random sequence generation, 44.4% of allocation concealment, 55.6% of blinding of participants, 66.7% of blinding of outcome assessment, 100% of incomplete outcome data, and 33.3% of selective reporting. There were not different results according to 6 items for the quality, respectively.

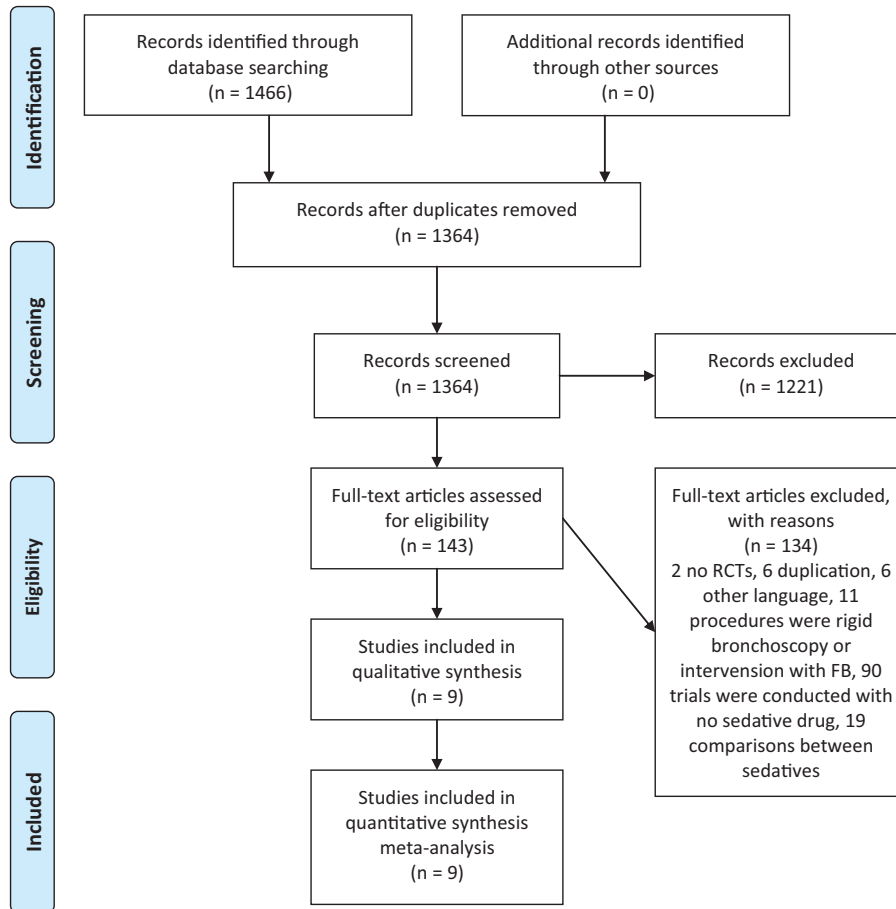


FIGURE 1. Flow diagram for identification of relevant trials. FB = flexible bronchoscopy, RCT = randomized controlled trial.

## Clinical Outcomes

### Efficacy

Six studies included data regarding the willingness of patients to repeat FB (Figure 2). Willingness to repeat was defined by an answer “yes” or “if needed” to the question “would you agree to a second procedure.” Patients who received moderate sedation seemed to have significantly more willing to repeat FB than those who did not receive sedation during FB (OR 2.30; 95% CI 1.11–4.73;  $P = 0.02$ ;  $I^2 = 22.5\%$ ). We investigated the atropine effects on willing to repeat as subgroup analysis. Willing to repeat FB was not different between sedation and no-sedation groups when atropine routinely injected in premedication of procedure in both groups (OR 1.95; 95% CI 0.75–5.08;  $P = 0.13$ ;  $I^2 = 16.5\%$ ). In contrast, willing to repeat FB was significantly more in sedation group than no-sedation group without atropine premedication (OR 7.25; 95% CI 1.01–52.00;  $P = 0.03$ ;  $I^2 = 8.1\%$ ).

In the comparison of sedation versus no-sedation, the pooled duration of FB tended to be shorter in sedation group than no-sedation group (SMD  $-0.21$ ; 95% CI  $-0.38$  to  $-0.03$ ;  $I^2 = 78.3\%$ ;  $P = 0.02$ ). In a subgroup including 3 trials<sup>12–15</sup> of midazolam versus placebo, the duration of FB also tended to be shorter with sedation than with placebo (SMD  $-0.40$ ; 95% CI  $-0.64$  to  $-0.17$ ;  $I^2 = 60.5\%$ ;  $P = 0.001$ ).

VAS for pain and cough was reported in 3 studies (Table 2). The VAS of pain and cough was better in the sedation group in both studies. In the study conducted by Viedma et al, a reverse VAS scale was used; the higher scale representing lesser pain and coughing during the test. We could not be pooling these data.

### Safety

Respiratory depression was monitored by pulse oximetry continuously. The SpO<sub>2</sub> during FB was not different between groups with sedation or no-sedation (SMD  $-0.14$ ; 95% CI  $-0.37$  to  $0.08$ ;  $P = 0.21$ ;  $I^2 = 49.9\%$ ; see Figure 3). There was no significant heterogeneity among the 4 trials ( $I^2 < 50\%$ ,  $P = 0.11$ ). The forest plot of SpO<sub>2</sub> showed different directions in SMD. This is consistent with our hypothesis that outcomes would differ according to routine supplemental oxygen. Subgroup analysis, wherein the groups were assigned according to the routine supplemental oxygen, showed that SpO<sub>2</sub> during FB was significantly different between subgroups under the increased homogeneity ( $I^2 = 0\%$ ,  $P = 0.02$ ). Moreover, the SpO<sub>2</sub> was significantly lower in sedation subgroup without supplemental oxygen than no-sedation group (SMD  $-0.45$ ; 95% CI  $-0.78$  to  $-0.11$ ;  $P = 0.01$ ;  $I^2 = 0.0\%$ ). In contrast, there was no difference in SpO<sub>2</sub> between the sedation subgroup with

**TABLE 1. Characteristics of Included Studies**

Author	Year	Study Country	Group 1 (n)				Group 2 (n)				Routinely O2 Supplement		Type of Procedure			
			Drug	Dose	No. of Patients	Age	No. of Male	Drug	No. of Patients	Age	No. of Male	Hypoxia Definition	Amount	Atropine	Questionnaires Time After BFS	Group 1
Rees, et al	1983	England	diazepam	10 mg IM	15	Not reported	Not reported	15	Not reported	15	Not reported	No	yes	1-3 hours		
Kolek, et al	1991	Czechoslovakia	midazolam	0.07 mg/kg IV	21	48.1	13	20	48.8	13	Not reported	No	yes	24 hrs	(0.6mg IM)	
Hatton, et al	1994	England	midazolam	70 ug/kg IV	51	Not reported	37	30	Not reported	30	Not reported	Yes	Not reported	6hrs	(0.5mg IM)	
Maltas, et al	1996	Canada	lorazepam	1-2 mg po	51	63±11	37	49	59±14	32	SaO2<90%	No	No	immediately	(0.6mg IM)	
Putinati, et al	1999	Italy	diazepam	5 and 15 mg IV	50	61±13	41	50	62±12	38	SaO2<90%	No	yes	3hrs	(0.5mg IM)	EB/brushing(28%), EB/Brushing(32%), routine(68%)
Won, et al	1999	South Korea	midazolam	5 mg IM	20	55±14.1	13	20	52±14.6	15	SaO2<90%	No	yes	immediately		washing(85%), brush(10%), biopsy(40%), routine(15%)
Gonzalez, et al	2003	Mexico	propofol	a bolus: 0.5-1 mg/kg -> bolus of 20 mg to maintain to same level	9	40±4*	7	9	46±5	6	SaO2<85%	Yes	face mask	1hr, 6hrs	(0.5mg IM)	110cc BAL; 100% of the patients
Viedma, et al	2010	Spain	midazolam	0.07-0.1 mg/kg IV	79	53.9±15.5*	25	73	59.6±13.4	22	SaO2<90%	Yes	oxygen delivery glasses of 4L/min	30 min		aspiration(37.5%), bronchial biopsy(23.6%), transbronchial biopsy(19.4%), blind FNAB(9.7%), BAL(44.4%), brush(27.7%)
Rolo, et al	2012	Portugal	midazolam	0.05 mg/kg IV	50	55±14.4	32	50	57.1±13.8	34	Not reported	Yes	Not reported	1 hr		110cc BAL; 100% of the patients

BFS = bronchoscopy, BAL = bronchoalveolar lavage, TBB = transbronchial biopsy, BB = bronchial brushing, EB = endobronchial, EBB = endobronchial biopsy, BW = bronchial washing, ILD = interstitial lung disease, BMI = body mass index, BIS = bispectral index, hs = hours, \*: glycopyrrolate, Values are given as mean (range or SD) for drug dose.

**TABLE 2.** The Sedative Agents Using in the Studies (Effectivity and Side Effect)

Author	Year	Group 1	Group 2	Effectivity of Sedatives Comparing to Control	Side effect of Sedatives Comparing to Control
Rees et al	1983	diazepam	saline	Less cough 11 vs 4 ( $P < 0.05$ )	Not reported
Kolek et al	1991	midazolam	saline	Willing to repeat BFS 95% vs 70% ( $P < 0.05$ )	Not reported
Hatton et al	1994	midazolam	saline	VAS (100 mm) for easy of procedure (ph) 19 vs 30 ( $P < 0.016$ ) VAS (100 mm) for willingness to repeat BFS (pt) 19 vs 8 ( $P < 0.936$ )	Not reported
Maltais et al	1996	lorazepam	placebo po	Willing to repeat BFS 57.1% vs 30.0% ( $P < 0.015$ )	Oxygen desaturations 1 vs 1
Putinati et al	1999	diazepam	Not reported	VAS (100 mm) for procedure tolerance score (pt) 14.75 vs 22.86 ( $P < 0.05$ )	Oxygen desaturations : 16 (17%), equally distributed in the two groups
Won et al	1999	midazolam	saline	Unpleasant feeling 16 vs 7	Oxygen desaturations 4 vs 5
Gonzalez et al	2003	propofol	Not reported	VAS(10mm) for pain score during BFS (pt) 0 vs 5 ( $P < 0.01$ ) VAS(10mm) for cough during BFS (pt) 5 vs 7 ( $P < 0.05$ )	Not reported
Viedma et al	2010	midazolam	saline	Pain during the test (pt)* 1.73 ± 1.15 vs 0.73 ± 0.87 ( $P = 0.0001$ ) Coughing during the test (pt)* 1.84 ± 1.13 1.2 ± 1.12 ( $P = 0.0001$ )	Oxygen desaturations 2 vs 0
Rolo et al	2012	midazolam	saline	Willing to repeat BFS 100% vs 82% ( $P < 0.003$ )	No significant changes in mean sO <sub>2</sub> level 97.0% vs 97.6%

BFS = bronchoscopy, VAS = visual analogue scale, ph = physician, pt = patient.  
\* Response scale (1 = a lot, 2 = quite a lot, 3 = somewhat, 4 = a little, 5 = very little).

supplemental oxygen and no-sedation group (SMD 0.10; 95% CI -0.20 to 0.40;  $P = 0.50$ ;  $I^2 = 0.0\%$ ). In the 4 selected studies, Begg funnel plot was symmetrical, and Egger test showed that  $P$  for bias was 0.59. The incidence of severe hypoxia was not different between sedation and no-sedation groups according to 6 trials (OR 0.86; 95% CI 0.42–1.73;  $P = 0.67$ ;  $I^2 = 0\%$ ). The events of hypoxia were no affected

by supplemental oxygen. Begg funnel plot was symmetrical, and Harbord test showed that  $P$  for bias was 0.67. Heart rate during FB was not different between groups regardless of atropine in 4 studies (SMD -0.07; 95% CI -0.29 to 0.16;  $P = 0.55$ ;  $I^2 = 67.7\%$ ). Systolic blood pressure during FB was investigated only one study (SMD -0.87; 95% CI -0.87 to -0.22;  $P = 0.001$ ).

**TABLE 3.** Methodological Quality of Trials Included Studies Based on Risk of Bias

Author	Year	Risk of Bias					
		Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Rees, et al	1983	unknown	low	low	low	low	unknown
Kolek, et al.	1991	unknown	unknown	unknown	low	low	unknown
Hatton, et al	1994	unknown	unknown	unknown	unknown	low	unknown
Maltais, et al	1996	unknown	low	low	low	low	low
Putinati, et al.	1999	unknown	unknown	high	unknown	low	unknown
Won, et al.	1999	high	unknown	low	low	low	unknown
Gonzalez, et al.	2003	low	low	low	low	low	low
Viedema, et al	2010	low	low	low	low	low	low
Rolo, et al.	2012	unknown	unknown	unknown	unknown	low	unknown

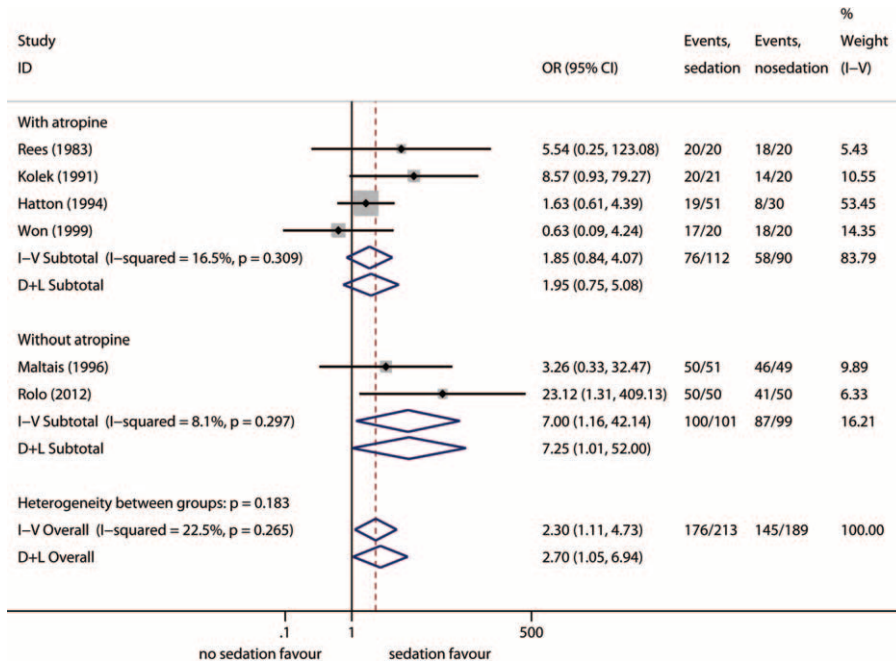


FIGURE 2. Pooled results of willingness to repeat flexible bronchoscopy between sedation and no-sedation.

**DISCUSSION**

This meta-analysis of RCTs indicates that moderate sedation during FB was associated with the increase in efficacy of willingness to repeat FB and shortening the procedural duration. In addition, there was no more complication in moderate sedation than no-sedation such as hypoxic events or significant desaturation.

The patients who need to FB are vulnerable to respiratory complications such as hypoxia. The sedative agents used for moderate sedation have the potential for respiratory depression. Particular attention should be paid to patients in whom oxygenation and ventilation may be difficult. According to the

guideline for procedural sedation in adults, supplemental oxygen is often recommended during procedural sedation to maintain oxygen reserves and prevent hypoxemia caused by hypoventilation. In the real field, supplying oxygen is different according to clinicians under moderate sedation. Supplemental oxygen during FB was just a concern for individual clinicians. In this meta-analysis, overall pooled effect of moderate sedation on oxygen saturation or the events of hypoxia did not show the difference compared with no-sedation. The respiratory complication seemed to be negligible. It was danger to have a hasty conclusion. Subgroup analysis to investigate the heterogenic factors revealed that moderate sedation without supplemental

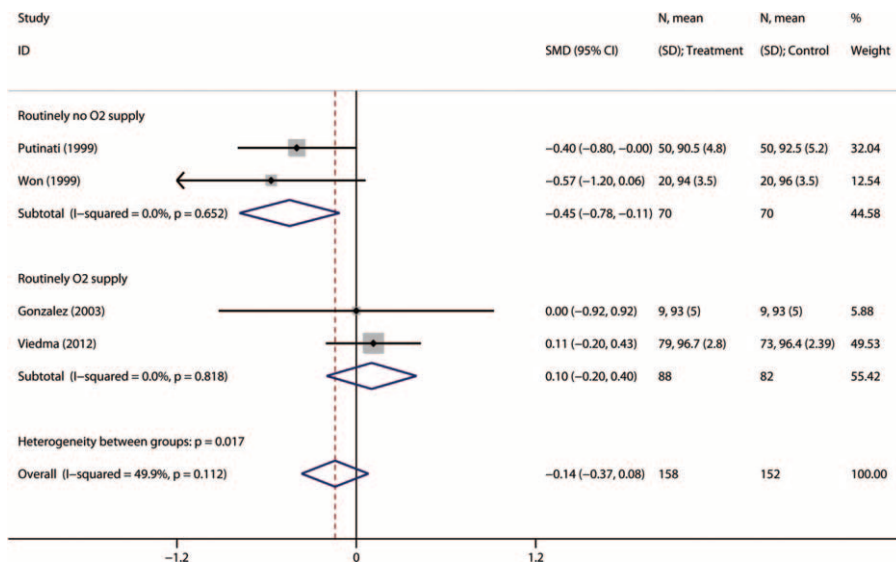


FIGURE 3. Pooled results of SpO<sub>2</sub> during flexible bronchoscopy between sedation and no-sedation.

oxygen might be high probability of desaturation. Our result might be the first evidence to show that routine supplemental oxygen is beneficial during FB under moderate sedation. Previous studies showed deep sedation or general anesthesia may be better than moderate sedation in cases with invasive procedures by bronchoscopy or rigid bronchoscopy.<sup>5</sup> This study is limited to cases with simple FB, in which moderate sedation may be comfortable and safe.

Although diagnostic results were equivocal regardless of sedation, there had been a negative stance because of a potential increase in cost for the sedation. As the experience of truly drug use during FB has increased, moderate sedation during FB has been truly implemented gradually.<sup>11</sup> In a recent survey, moderate sedation has been used by more than half.<sup>20</sup> Studies with patient-centered outcomes were few and were inconsistent in measures. Most studies mainly investigated the willingness to repeat FB as patient-centered outcome. Willingness to repeat FB was nonsense word. Strictly, willingness to repeat has not represented patients' comfort. The patients are obligated to choice either repetition to FB or lung biopsy under general anesthesia if they were not diagnosed yet. However, willingness to repeat FB was a different meaning to patients with benign disease like patients who transplanted lung. In this situation, moderate sedation might be helpful and effective to patients according to this meta-analysis.

According to current consensus, using anticholinergics (atropine or glycopyrrolate) at pre-FB is discouraged. Atropine did not produce a clinically meaningful improvement in lung function or decrease in bronchial secretions. Atropine has a sedative effect minimally. Before American College of Chest Physicians consensus, many clinicians used to administer atropine for premedication in FB. In this meta-analysis, willingness to repeat FB was different whether administered premedication of atropine or not. When atropine did not administer before FB, the effect of moderate sedation on willingness to repeat FB was significantly more than no-sedation group (OR 7.00,  $P=0.034$ ). In the situation without atropine during FB, moderate sedation would be helpful in patient's comfort.

Our study has several limitations in the evidences supporting the use of sedation in FB. First, we had to consider the selection bias. Only 4 among 9 studies could be included in the summary statistics because all studied did not report the outcome for oxygen saturation. Most studies aimed to investigate the efficacy such as tolerance or comfort. Some studies just mentioned as no significant complication statistically, instead of the exact data. We tried to overcome this problem by analyzing the publication bias. There was no publication bias statistically. Second, in this study, sedation would help to reduce the duration in FB. However, this finding also had a significant heterogeneity. This heterogeneity might be related to the experience of the bronchoscopists. There was no precise information about the experience of bronchoscopists. Also, the type of procedures during FB would be various. When we performed the bronchoscopic biopsy, some bronchoscopists obtained 3 or 4 pieces; others obtained >4 pieces. To exploring these factors, meta-regression would be needed. Meta-regression is possible to analyze with >10 studies. Therefore, our findings for duration should be interpreted cautiously. Third, we analyzed the willingness to repeat FB as the efficacy for moderate sedation. Strictly speaking, the efficacy should be diagnostic yield or direct method as VAS tool for patient's comfort. There is a paucity of study using moderate sedation with diagnostic yield or VAS tool. Further trials are required to investigate the efficacy as diagnostic yield and direct

measurement for the comfort with consistent VAS scale and the same questionnaire. Fourth, sedative drugs were just 2 categories: benzodiazepine and propofol in this meta-analysis. The various sedative drugs are used in the real field, and there has already been a review article about pharmacological principles of these drugs during the bronchoscopy.<sup>21</sup> Further trials with various sedative are required to investigate the safety and the best drug of choice. Fifth, it is an important issue of safety who administer the sedative drugs. Studies enrolled in this meta-analysis did not stipulate. We could not guarantee safety whoever administered the sedative drugs in the procedural room. Sixth, there was no compensation for the wide variation in the level of training and individual commitment to proficiency (Table 1). These things obscured the interpretation of incidence of complications. Nonetheless, the results of pooled analyses in this study were considered significant if the  $I^2$  was <30% after evaluating heterogeneity with  $I^2$  statistics.

In conclusion, according to this meta-analysis, moderate sedation in FB would be useful in patients who will require repeated bronchoscopies as well as safe in respiratory depression. To our knowledge, although the various sedative drugs are already used in the real field, this analysis was the first attempt to quantify objective results. We anticipate more definite and studies designed to elucidate standardized outcomes for moderate sedation in FB.

## REFERENCES

- Smyth CM, Stead RJ. Survey of flexible fibreoptic bronchoscopy in the United Kingdom. *Eur Respir J*. 2002;19:458–463.
- Schlatter L, Pflimlin E, Fehrke B, et al. Propofol versus propofol plus hydrocodone for flexible bronchoscopy: a randomised study. *Eur Respir J*. 2011;38:529–537.
- Stolz D, Chhajed P, Leuppi J, et al. Cough suppression during flexible bronchoscopy using combined sedation with midazolam and hydrocodone: a randomised, double blind, placebo controlled trial. *Thorax*. 2004;59:773–776.
- Poi P, Chuah S, Srinivas P, et al. Common fears of patients undergoing bronchoscopy. *Eur Respir J*. 1998;11:1147–1149.
- Ost DE, Ernst A, Grosu HB, et al. Therapeutic bronchoscopy for malignant central airway obstruction: success rates and impact on dyspnea and quality of life. *Chest*. 2015;147:1282–1298.
- Dreher M, Ekkernkamp E, Storre JH, et al. Sedation during flexible bronchoscopy in patients with pre-existing respiratory failure: Midazolam versus Midazolam plus Alfentanil. *Respiration*. 2010;79:307–314.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269.
- Harris R, Bradburn M, Deeks J, et al. Meta: fixed-and random-effects meta-analysis. *Stata J*. 2008;8:3–28.
- Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
- Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
- Hatton MQ, Allen MB, Vathenen AS, et al. Does sedation help in fibreoptic bronchoscopy? *BMJ*. 1994;309:1206–1207.
- Maltais F, Laberge F, Laviolette M. A randomized, double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. *Chest*. 1996;109:1195–1198.

13. Putinati S, Ballerin L, Corbetta L, et al. Patient satisfaction with conscious sedation for bronchoscopy. *Chest*. 1999;115:1437–1440.
14. Rolo R, Mota PC, Coelho F, et al. Sedation with midazolam in flexible bronchoscopy—a prospective study. *Rev Port Pneumol*. 2012;18:226–232.
15. Won JH, Park JY, Seung Ick C, et al. Is premedication necessary for outpatient fiberoptic bronchoscopy. *Tuberc Respir Dis*. 1999;46:251–259.
16. Rees PJ, Hay JG, Webb JR. Premedication for fibreoptic bronchoscopy. *Thorax*. 1983;38:624–627.
17. Kolek V, Jezdinsky J. Comparative study of midazolam and diazepam in premedication of bronchoscopy. *Acta Univ Palacki Olomuc Fac Med*. 1991;131:233–241.
18. Gonzalez R, De-La-Rosa-Ramirez I, Maldonado-Hernandez A, et al. Should patients undergoing a bronchoscopy be sedated? *Acta Anaesthesiol Scand*. 2003;47:411–415.
19. Cases Viedma E, Perez Pallares J, Martinez Garcia MA, et al. [A randomised study of midazolam for sedation in flexible bronchoscopy]. *Arch Bronconeumol*. 2010;46:302–309.
20. Prakash UB, Offord KP, Stubbs SE. Bronchoscopy in North America: the ACCP survey. *Chest*. 1991;100:1668–1675.
21. Goudra BG, Singh PM, Borle A, et al. Anesthesia for advanced bronchoscopic procedures: state-of-the-art review. *Lung*. 2015;193:453–465.