

# The impact of alfentanil supplementation on the sedation of bronchoscopy

## A meta-analysis of randomized controlled trials

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### Abstract

**Background:** The efficacy of alfentanil supplementation for the sedation of bronchoscopy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of alfentanil supplementation on the sedation during bronchoscopy.

**Methods:** We search PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases through December 2019 for randomized controlled trials (RCTs) assessing the effect of alfentanil supplementation versus placebo for the sedation during bronchoscopy. This meta-analysis is performed using the random-effect model.

**Results:** Five RCTs are included in the meta-analysis. Overall, compared with control group for bronchoscopy, alfentanil supplementation is associated with significantly reduced coughing scores (Std. MD = -0.55; 95% CI = -0.96 to -0.14;  $P = 0.009$ ) and dose of propofol (Std. MD = -0.34; 95% CI = -0.64 to -0.04;  $P = 0.03$ ), but reveals the increase in hypoxemia (RR = 1.56; 95% CI = 1.17 to 2.08;  $P = 0.002$ ).

**Conclusions:** Alfentanil supplementation benefits to reduce coughing scores and dose of propofol for bronchoscopy, but increases the incidence of hypoxemia. The use of alfentanil supplementation for bronchoscopy should be with caution.

**Abbreviations:** CI = confidence interval, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, SMD = standard mean difference.

**Keywords:** alfentanil supplementation, bronchoscopy, meta-analysis, randomized controlled trials, sedation

## 1. Introduction

Bronchoscopy is widely used for the diagnosis and treatment of pulmonary disease,<sup>[1,2]</sup> but commonly results in pain, anxiety, cough, shortness of breath and other chest discomforts.<sup>[3-5]</sup> The proper delivery of sedation is crucial to ensure patient comfort, and minimize the risk during bronchoscopy, especially for complex and longer procedures.<sup>[6]</sup> The combination of opioids with other sedatives has a synergistic effect on analgesia, relieving coughing, and sedation.<sup>[7-9]</sup> Good cough control is very important for flexible bronchoscopy with long procedure time.<sup>[10]</sup>

Sedatives are evaluated by the best pharmacokinetic characteristics such as fast onset, short action and rapid recovery. Fentanyl has emerged as an increasingly important drug for the sedation of bronchoscopy.<sup>[11,12]</sup> 50 µg of fentanyl supplementation is found to produce better sedation, patient and operator satisfaction compared to placebo during bronchoscopy.<sup>[13]</sup> Alfentanil and propofol have the potential in fast onset, quick

recovery and the reduction in hypoxemia. They are found to be ideal for the sedation of bronchoscopy and provide good bronchoscopist satisfaction and patient tolerance.<sup>[14,15]</sup>

However, the efficacy of alfentanil supplementation for the sedation of bronchoscopy has not been well established. In a prospective randomized study analyzing 80 patients undergoing bronchoscopy, patients receiving 20 mcg/kg alfentanil supplementation was associated with substantially reduced coughing scores than control intervention.<sup>[16]</sup> In contrast, no statistical difference of coughing scores and bronchoscopy score remained between alfentanil supplementation and control intervention.<sup>[17]</sup> This systematic review and meta-analysis of RCTs aims to compare the sedative efficacy of alfentanil supplementation for bronchoscopy.

## 2. Materials and Methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously

YH and MF contributed equally.

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published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).<sup>[18]</sup>

**2.1. Search strategy and study selection**

Two investigators have independently searched the following databases (inception to December 2019): PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: fentanyl, and bronchoscopy. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients undergoing bronchoscopy; (ii) intervention: alfentanil supplementation; (iii) comparison: placebo; (iv) study design: RCT. The sedation with alfentanil supplementation was performed by anesthesiologists.

**2.2. Data extraction and outcome measures**

We have extracted the following information: author, number of patients, age, male, weight, current smoker and detail methods in each group etc. Data have been extracted independently by 2 investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary.

The primary outcome is coughing scores. Secondary outcomes include dose of propofol and hypoxemia.

**2.3. Quality assessment in individual studies**

Methodological quality of the included studies is independently evaluated using the modified Jadad scale.<sup>[19]</sup> There are 3 items for Jadad scale: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score  $\leq 2$  is considered to be of low quality. If the Jadad score  $\geq 3$ , the study is thought to be of high quality.<sup>[20]</sup>

**2.4. Statistical analysis**

We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (dose of propofol and coughing scores) risk ratios (RRs) with 95% CIs for dichotomous outcomes (hypoxemia). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the  $I^2$  statistic, and  $I^2 > 50\%$  indicates significant heterogeneity.<sup>[21]</sup> Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting 1 study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

**3. Results**

**3.1. Literature search, study characteristics, and quality assessment**

A detailed flowchart of the search and selection results is shown in Figure 1. 175 potentially relevant articles are identified

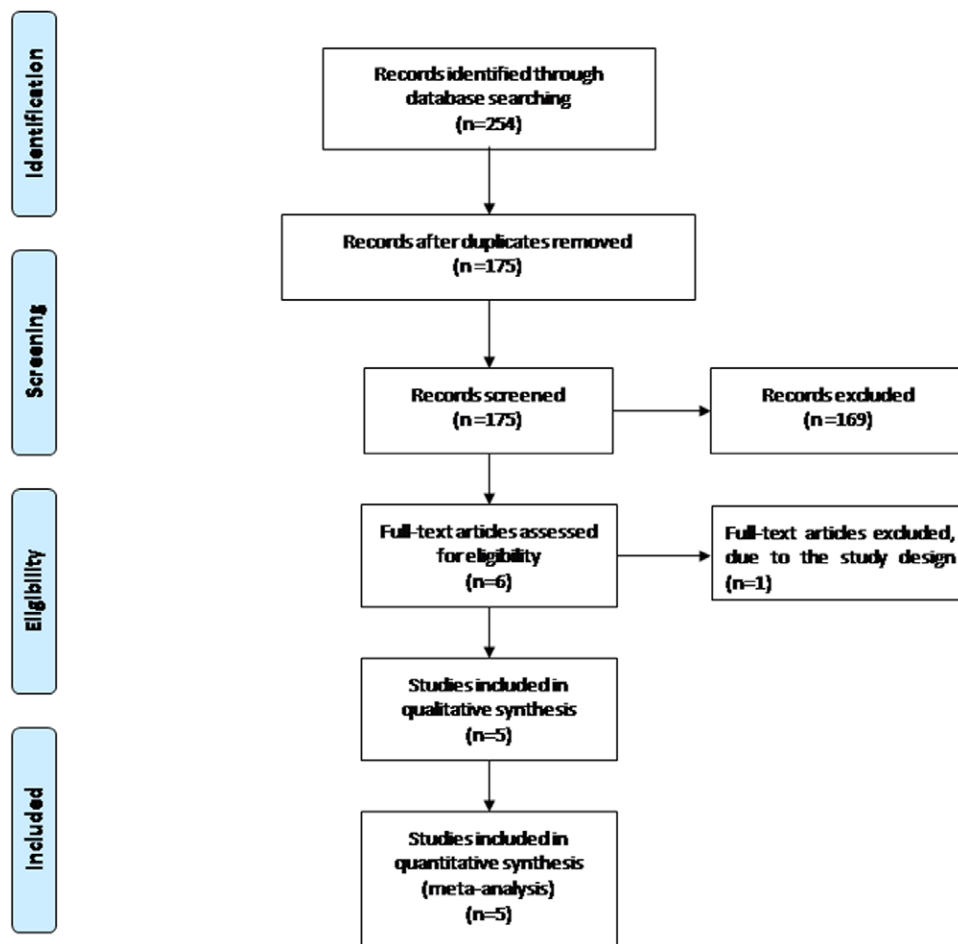


Figure 1. Flow diagram of study searching and selection process.

**Table 1**  
**Characteristics of included studies.**

No.	Author	Alfentanil group					Control group							
		Number	Age (yr)	Male (n)	Weight (kg)	Current smoker (n)	Number	Age (yr)	Male (n)	Weight (kg)	Current smoker (n)			
1	Riachy 2018	55	18-70	24	-	29	25 ml of lidocaine 1% by bronchoscopy plus slow intravenous infusion of saline serum 0.9% with electronic pump over 10 minutes plus slow intravenous infusion of alfentanil 10 µg/kg over 5 seconds	54	18-70	30	-	32	25 ml of lidocaine 1% by bronchoscopy plus slow intravenous infusion of saline serum 0.9% with electronic pump over 10 minutes plus slow intravenous infusion of 2 ml saline serum 0.9% over 5 seconds	3
2	Hsieh 2016	36	60.9±13.9	13	62.3±9.0	11	Alfentanil 5 µg/kg, 2 minutes before propofol administration	34	62.2±11.1	12	60.8±12.0	6	Propofol administration	4
3	Yoon 2011	32	58.8±14.3	14	62.0±10.0	-	Propofol 8.3 mg/kg plus alfentanil 1000 µg	32	57.3±11.6	15	62.1±12.5	-	Propofol 8.3 mg/ml	4
4	Leite 2008	20	54.6±14.3	3	-	-	200 mg topical lidocaine and 20 mcg/kg alfentanil	20	60.3±12.7	8	-	-	200 mg topical lidocaine	3
5	Agnew 2003	19	69 (60-72)	6	75 (67-85)	-	A bolus of 10 µg/kg of alfentanil	20	65 (57-71)	5	74 (62-82)	-	Placebo	3

initially. Finally, 5 RCTs that meet our inclusion criteria are included in the meta-analysis.

The baseline characteristics of the 5 eligible RCTs in the meta-analysis are summarized in Table 1. The 5 studies are published between 2003 and 2018, and sample sizes range from 39 to 109 with a total of 322. The doses of alfentanil range from 10 to 20 µg/kg.

Among the 5 studies included here, 3 studies report dose of propofol, 3 studies report coughing scores, and 3 studies report hypoxemia. Jadad scores of the 5 included studies vary from 3 to 4, and all 5 studies are considered to be high-quality ones according to quality assessment.

### 3.2. Primary outcome: coughing scores

This outcome data is analyzed with the random-effects model, and compared to control group for bronchoscopy, alfentanil supplementation is associated with significantly reduced coughing scores (Std. MD = -0.55; 95% CI = -0.96 to -0.14; *P* = 0.009), with no heterogeneity among the studies (*I*<sup>2</sup> = 52%, heterogeneity *P* = 0.12) (Fig. 2).

### 3.3. Sensitivity analysis

Significant heterogeneity is observed among the included studies for coughing scores. After excluding the study conducted by Leite,<sup>[16]</sup> there is no heterogeneity remained (*I*<sup>2</sup> = 0%, heterogeneity *P* = 0.42). The results reveal that alfentanil supplementation can still substantially reduce coughing scores (Std. MD = -0.37; 95% CI = -0.67 to -0.08; *P* = 0.01).

### 3.4. Secondary outcomes

In comparison with control group for bronchoscopy, alfentanil supplementation can substantially decrease the dose of propofol (Std. MD = -0.34; 95% CI = -0.64 to -0.04; *P* = 0.03; Fig. 3),

but exerts the increase in hypoxemia (RR = 1.56; 95% CI = 1.17 to 2.08; *P* = 0.002; Fig. 4).

## 4. Discussion

Our meta-analysis suggests that alfentanil supplementation is associated with remarkable decrease in the coughing scores and dose of propofol than control intervention for the sedation of bronchoscopy, but leads to the increase in the incidence of hypoxemia.

Cough widely occurs in patients undergoing bronchoscopy, and the administration of alfentanil with other sedatives produces a synergistic effect on analgesia, relieving coughing and sedation.<sup>[8,22,23]</sup> Alfentanil and propofol have been proven to be ideal for the sedation of bronchoscopy.<sup>[14,15]</sup> The incidence of hypoxemic events during propofol sedation for bronchoscopy is estimated to be about 30% to 40%.<sup>[15,24,25]</sup> Around 14% to 18% of hypoxemic events are present during induction.<sup>[15,26]</sup> Alfentanil supplementation is found to significantly reduce the coughing scores and dose of propofol than control intervention for bronchoscopy.

One-third of the patients suffer from some level of anxiety before flexible bronchoscopy in, and require the need for sedation.<sup>[27-29]</sup> Patient comfort and allaying anxiety are desirable during the procedures of bronchoscopy.<sup>[10,30,31]</sup> In 1 RCT, fentanyl in combination with midazolam resulted in obvious increase in the level of sedation for patients with bronchoscopy.<sup>[13]</sup> Alfentanil supplementation before propofol administration was proven to substantially decrease induction time and improve sedation levels during bronchoscopy.<sup>[17,32]</sup>

In addition, it is reported that alfentanil supplementation can reduce the injection pain related to propofol administration.<sup>[33]</sup> Some studies revealed some complications such as transient hypotension and significant oxygen desaturation during the sedation using fentanyl.<sup>[13]</sup> However, the increase in hypoxemia after alfentanil supplementation is observed than

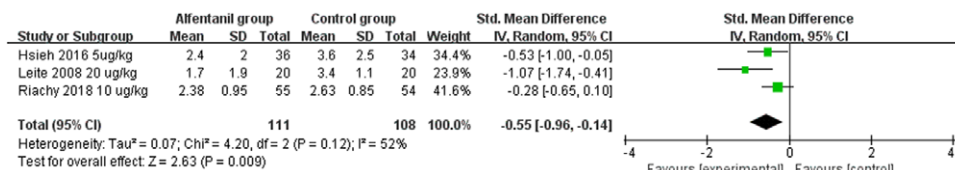


Figure 2. Forest plot for the meta-analysis of coughing scores. Alfentanil supplementation is associated with significantly reduced coughing scores than control group.

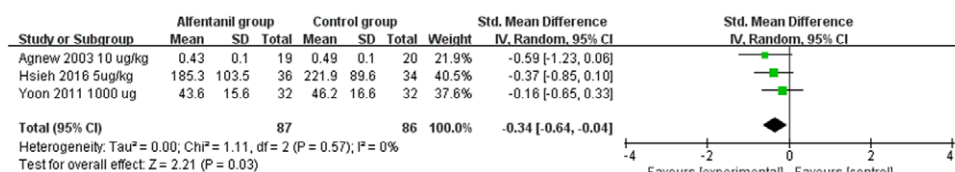


Figure 3. Forest plot for the meta-analysis of dose of propofol. Alfentanil supplementation is associated with significantly reduced dose of propofol than control group.

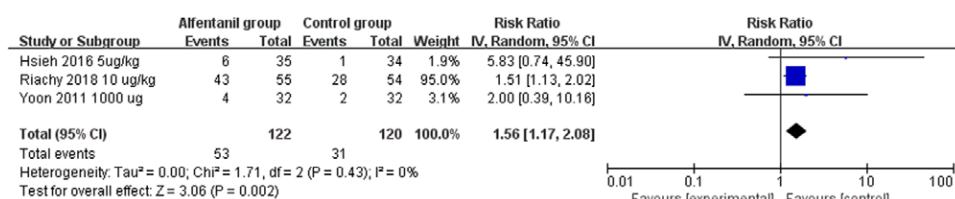


Figure 4. Forest plot for the meta-analysis of hypoxemia. Alfentanil supplementation is associated with higher incidence of hypoxemia than control group.

control intervention for bronchoscopy in this meta-analysis. In addition, 1 included RCT reported that alfentanil supplementation could obvious increase the respiratory depression ( $0.6 \pm 1.5$ ) compared to control group ( $0.0 \pm 0.0$ ) for patients undergoing bronchoscopy.<sup>[16]</sup> These indicate that the safety of alfentanil supplementation should be carefully assessed and concerned.

Regarding the sensitivity analysis, there is significant heterogeneity for coughing scores and no heterogeneity is observed after excluding the study conducted by Leite<sup>[16]</sup> ( $I^2 = 0\%$ , heterogeneity  $P = 0.42$ ) in which alfentanil is used at the dose of 20 mcg/kg. The remaining 2 studies reported alfentanil 10 mcg/kg<sup>[17]</sup> and 5 mcg/kg.<sup>[32]</sup> The results find that alfentanil supplementation is still associated with substantially reduced coughing scores (Std. MD =  $-0.37$ ; 95% CI =  $-0.67$  to  $-0.08$ ;  $P = 0.01$ ) than control intervention for bronchoscopy. This significant heterogeneity may be caused by the dose of alfentanil supplementation and combination methods.

There are several limitations that should be taken into consideration. Firstly, our analysis is based on 5 RCTs, and 4 of them have a relatively small sample size ( $n < 100$ ). These may lead to overestimation of the treatment effect in smaller trials. More RCTs with large sample size should be conducted to investigate this issue. Next, there is significant heterogeneity, which may result from different doses and combination of alfentanil supplementation. Finally, it is not feasible to perform some significant index such as sedation level, and patient satisfaction based on current studies.

## 5. Conclusions

Although alfentanil supplementation may provide additional benefits for the sedation of bronchoscopy, the increased hypoxemia should be concerned. The use of alfentanil supplementation for bronchoscopy should be with caution.

## Author contributions

The authors contribute equally.

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