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Review Article

The efficacy of fentanyl supplementation for the sedation of bronchoscopy: a meta-analysis of randomized controlled trials

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Abstract: Introduction: The efficacy of fentanyl supplementation for sedation of bronchoscopy remains controversial. A systematic review and meta-analysis was thus conducted to explore the influence of fentanyl supplementation on the sedation during bronchoscopy. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were searched for dates through October 2018 for randomized controlled trials (RCTs) assessing the effect of fentanyl supplementation versus placebo for the sedation during bronchoscopy. This meta-analysis was performed using the random-effect model. Results: Five RCTs involving 379 patients are included in the meta-analysis. Overall, compared with control group for bronchoscopy, fentanyl supplementation exhibits no important influence on sedation scores (Std. MD=-0.09; 95% CI=-0.34 to 0.16; P=0.49), heat rate (Std. MD=-0.07; 95% CI=-0.38 to 0.24; P=0.67), oxygen saturation (Std. MD=-0.50; 95% CI=-1.47 to 0.47; P=0.32), and hypoxia (RR=2.98; 95% CI=0.91 to 0.93; P=0.07), but shows the positive effect on cough (RR=0.84; 95% CI=0.71 to 0.99; P=0.04). Conclusions: Fentanyl supplementation may provide some benefits for bronchoscopy.

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

Introduction

Bronchoscopy has become the most frequently performed procedure in clinical practice for diagnosis and treatment of pulmonary disease [1-3]. Patients often suffer from sore nose and throat, cough, shortness of breath and other chest discomfort during the bronchoscopy [4-6]. Interventional procedures using flexible bronchoscopes have become complex, and may need long procedure time and good cough control [7]. The sedation/anesthesia of bronchoscopy should be monitored in order to attenuate the stress, reduce the complications and simplify the procedure [8].

Good sedation is crucial for patients' safety and satisfaction [9]. Sedatives are determined by the best pharmacokinetic characteristics such as fast onset, short action, and rapid recovery. A variety of sedatives have been developed including benzodiazepines, opioids, propofol, and dexmedetomidine etc [9-11]. Many studies find that fentanyl has emerged as an increasingly important drug for the sedation of bronchoscopy [12, 13]. For instance, 1 ml (50 μg) of fentanyl supplementation results in better sedation, patient and operator satisfaction compared to placebo during bronchoscopy [14].

However, the efficacy of fentanyl supplementation for bronchoscopy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [14-17]. With accumulating evidence, a systematic review and meta-analysis of RCTs was performed in this study to compare the efficacy of fentanyl supplementation versus placebo for bronchoscopy.

Materials and methods

Ethics approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis

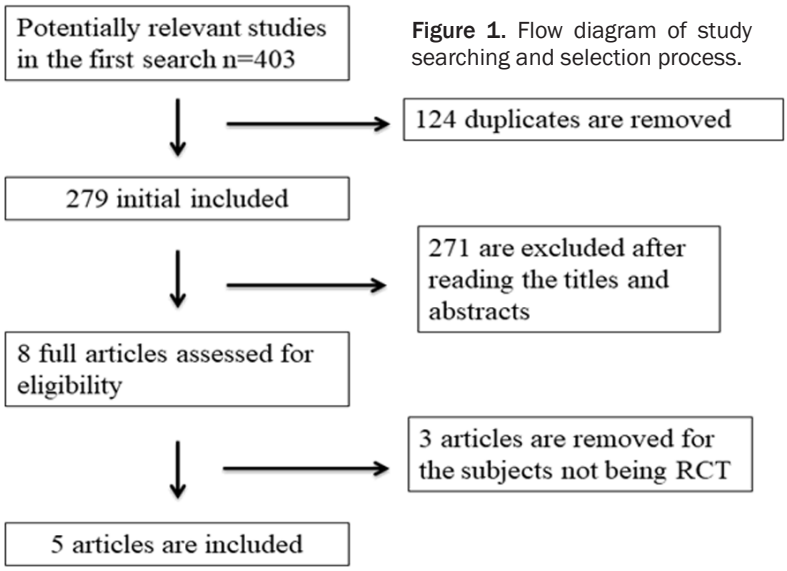

Figure 1. Flow diagram of study searching and selection process.

were conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [18].

Search strategy and study selection

Two investigators have independently searched the following databases (inception to October 2018): PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: fentanyl, and bronchoscopy. Reference lists of the screened full-text studies to identify other potentially eligible trials were also checked.

The inclusion selection criteria were as follows: (i) population: patients undergoing bronchoscopy; (ii) intervention: fentanyl supplementation; (iii) comparison: placebo; (iv) study design: RCT.

Data extraction and outcome measures

The following information was extracted: author, number of patients, age, male, weight or body mass index, current smoking status, and detail methods in each group etc. Data was extracted independently by two investigators, and discrepancies were resolved by consensus. The corresponding author was also contacted to obtain data when necessary.

The primary outcome was sedation scores. Secondary outcomes include heat rate, oxygen saturation, hypoxia, and cough.

Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [19]. 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 ≤2 is considered to be of low quality. If the Jadad score ≥3, the study is thought to be of high quality [20].

Statistical analysis

The standard mean difference (Std. MD) with 95% confidence interval (CI) was estimated for continuous outcomes (sedation scores, heat rate, and oxygen saturation) risk ratios (RRs) with 95% CIs for dichotomous outcomes (hypoxia and cough). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and I^2>50% indicates significant heterogeneity [21]. Whenever significant heterogeneity was present, potential sources of heterogeneity were searched via omitting one 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).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results are shown in **Figure 1** with 403 potentially relevant articles being identified initially. Finally, five RCTs that meet the inclusion criteria were included in the meta-analysis [14-17, 22].

The baseline characteristics of the five eligible RCTs in the meta-analysis are summarized in **Table 1**. The five studies are published between 2011 and 2018, and sample sizes range from 40 to 109 with a total of 379. The drug types of

Table 1. Characteristics of included studies

NO.	Author	Fentanyl group						Control group						Jada scores
		Number	Age (years)	Male (n)	Body mass index (kg/m^2) or weight (kg)	Current smoker (n)	Methods	Number	Age (years)	Male (n)	Body mass index (kg/m^2) or weight (kg)	Current smoker (n)	Methods	
1	Riachy 2018	55	18-70	24	-	29	25 ml of lidocaine 1% by bronchoscopy 1 slow intravenous infusion of saline serum 0.9% with electronic pump over 10 minutes 1 slow intravenous infusion of alfentanil 10 mcg/kg over 5 seconds	54	18-70	30	-	32	25 ml of lidocaine 1% by bronchoscopy 1 slow intravenous infusion of saline serum 0.9% with electronic pump over 10 minutes 1 slow intravenous infusion of 2 ml saline serum 0.9% over 5 seconds	3
2	Prabhudev 2017	48	52 (42.25-62.75), median (interquartile range).	31	20.5 (17.45-23.37) kg/m^2	4	Midazolam 0.035 mg/kg diluted in normal saline to a volume of 5 ml and 1 ml (50 μg) of fentanyl	48	50.5 (39.25-59.25), median (interquartile range)	33	19.69 (17.62-22.75) kg/m^2	4	Midazolam 0.035 mg/kg diluted in normal saline to a volume of 5 ml	5
3	Hsieh 2016	36	60.9±13.9	24	23.5±3.3 kg/m^2	11	Alfentanil 5 mg/kg was given 2 minutes before the administration of propofol	34	62.2±11.1	21	23.2±3.7 kg/m^2	6	Normal saline was given 2 minutes and immediately before the administration of propofol	4
4	Quintard 2012	20	51±17	17	78±14 kg	-	Remifentanil given at a target effect site concentration of 4 ng/ml	20	56±18	18	72±29 kg	-	Placebo	4
5	Yoon 2011	32	58.8±14.3	18	62.0±10.0 kg	-	100 mg of propofol and 1000 mg of alfentanil	32	57.3±11.6	17	62.1±12.5 kg	-	100 mg of propofol plus 2 ml of saline	4

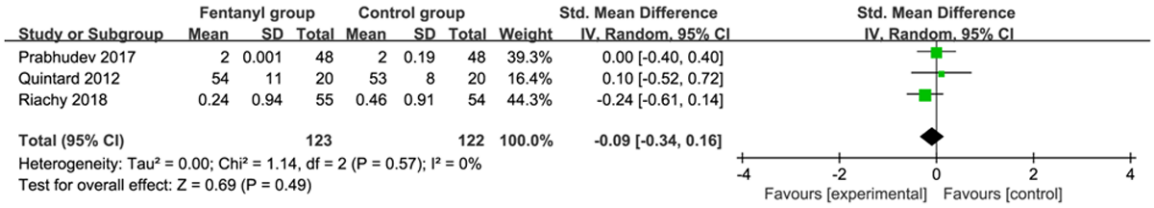

Figure 2. Forest plot for the meta-analysis of sedation scores.

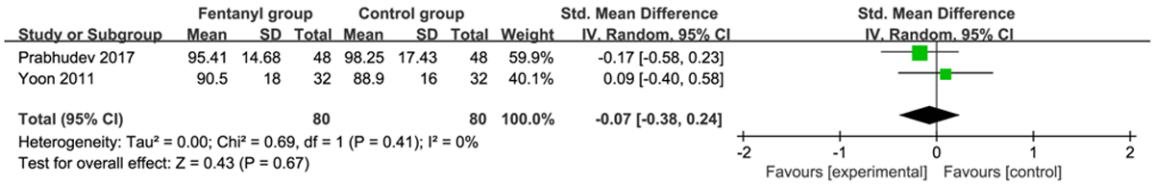

Figure 3. Forest plot for the meta-analysis of heat rate.

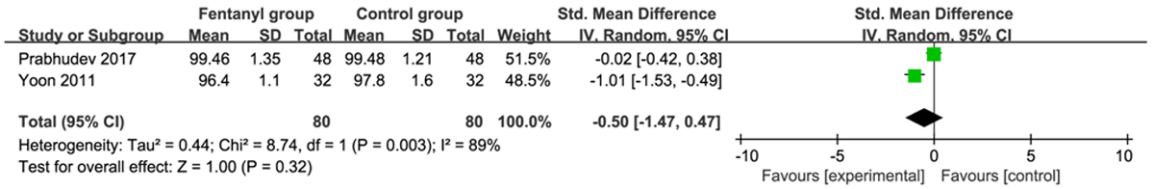

Figure 4. Forest plot for the meta-analysis of oxygen saturation (%).

fentanyl include alfentanil, and remifentanil, and their doses are different in each RCT.

Among the five studies included here, three studies report sedation scores [14, 15, 17], two studies report heat rate and oxygen saturation [14, 22], four studies report hypoxia [14-16, 22], and two studies report cough [14, 15]. Jadad scores of the five included studies vary from 3 to 5, and all five studies are considered to be high-quality ones according to quality assessment.

Primary outcome: sedation scores

This outcome data was analyzed with the random-effects model, and compared to control group for bronchoscopy, fentanyl supplementation exhibits no obvious effect on sedation scores (Std. MD=-0.09; 95% CI=-0.34 to 0.16; P=0.49), with no heterogeneity among the studies (I^2=0%, heterogeneity P=0.57) (**Figure 2**).

Sensitivity analysis

No heterogeneity was observed among the included studies for sedation scores, and thus sensitivity analysis via omitting one study in turn to detect the heterogeneity was not performed.

Secondary outcomes

In comparison with the control group for bronchoscopy, fentanyl supplementation exerted no significant impact on heat rate (Std. MD=-0.07; 95% CI=-0.38 to 0.24; P=0.67; **Figure 3**), oxygen saturation (Std. MD=-0.50; 95% CI=-1.47 to 0.47; P=0.32; **Figure 4**), hypoxia (RR=2.98; 95% CI=0.91 to 0.93; P=0.07; **Figure 5**), but was associated with substantially reduced cough (RR=0.84; 95% CI=0.71 to 0.99; P=0.04; **Figure 6**).

Discussion

Some level of anxiety before flexible bronchoscopy has been reported in one-third of the patients, and requires the need for analgesics [23-25]. Patient comfort and allaying anxiety are desirable by the use of sedation [7, 26, 27]. Sedation drugs are widely used for bronchoscopy, but it is not uniform with regard to class, and dose of drugs [28, 29]. Guidelines suggest sedation preferable but not mandatory, and

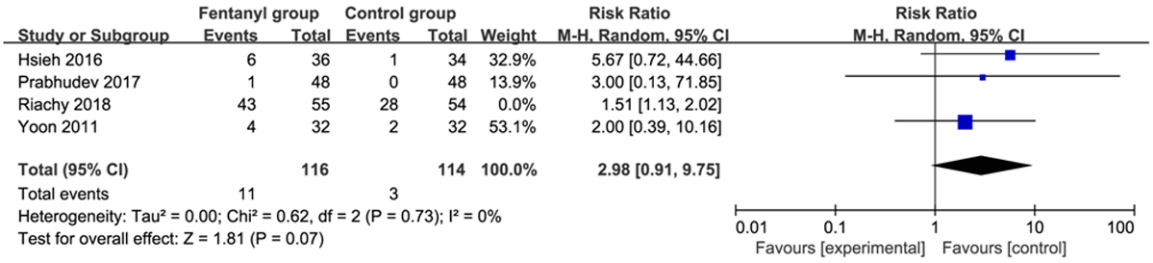

Figure 5. Forest plot for the meta-analysis of hypoxia.

Figure 6. Forest plot for the meta-analysis of cough.

patients' preference is advised to seek in this case [9, 13]. In one RCT, fentanyl supplementation to midazolam results in obvious increase in the level of sedation for patients with bronchoscopy [14]. This meta-analysis concludes that fentanyl supplementation has no strong connection with the level of sedation for bronchoscopy.

In some study, some complications such transient hypotension and significant oxygen desaturation may occur during the sedation using midazolam or fentanyl [14]. There was no statistical difference between two groups with regards to heat rate, oxygen saturation and hypoxia in our meta-analysis. Indeed, these episodes can be managed without any serious consequences. Combinations of sedatives may cause excessive sedation, but no significant increase in adverse events are observed [29, 30]. In addition, the incidence of cough is found to be obviously lower in fentanyl supplementation group than that in control group based on the results of our meta-analysis.

Patient satisfaction and tolerance of the procedure is an important aspect when performing flexible bronchoscopy. It is believed that sedation is one of the important determinants of patient tolerance and satisfaction, and inadequacy of sedation results in unpleasant feeling in two-thirds of patients, and the decline to a repeat procedure in about one-fourth patients [31]. Better satisfaction can be achieved among patients receiving good sedation compared to non-sedated patients [32, 33]. One RCT reports that 1 ml (50 μg) of fentanyl supplementation to midazolam 0.035 mg/kg diluted in normal saline shows the marked increase in patient and operator satisfaction in patients with bronchoscopy [14].

This meta-analysis has several potential limitations. First, it is based on five RCTs, and four 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, although there was no heterogeneity for the analysis of sedation scores, many factors such as different types, doses, and combination of fentanyl supplementation may have some valuable effect on the pooling results. In addition, some significant index such as patient satisfaction and hospital stay cannot be conducted for the meta-analysis based on current studies. Finally, various operation procedures during bronchoscopy may also affect the efficacy assessment of fentanyl supplementation.

Conclusions

Fentanyl supplementation may provide additional benefits for bronchoscopy, but more RCTs should be performed to explore this issue.

Disclosure of conflict of interest

None.

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