Systematic Review and Meta-Analysis

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The comparison of propofol and midazolam for bronchoscopy

A meta-analysis of randomized controlled studies

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Abstract

Background: Propofol and midazolam are widely used for the sedation of bronchoscopy. This systematic review and meta-analysis is conducted to compare the efficacy of propofol and midazolam for bronchoscopy.

Methods: The databases including PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases are systematically searched for collecting the randomized controlled trials (RCTs) regarding the efficacy of propofol and midazolam for bronchoscopy.

Results: This meta-analysis has included 4 RCTs. Compared with midazolam intervention in patients undergoing bronchoscopy, propofol intervention is associated with remarkably reduced recovery time [standard mean difference (SMD) = −0.74; 95% confidence interval (95% CI) = −1.04 to −0.45; $P < .00001$], but demonstrates no significant impact on operation time (SMD = −0.01; 95% CI = −0.16 to 0.13; $P = .87$), induction time (SMD = −0.58; 95% CI = −1.19 to 0.03; $P = .06$), lowest oxyhemoglobin saturation (SpO_2, SMD = 0.24; 95% CI = −0.09 to 0.58; $P = .15$), SpO_2 <90% [risk ratio (RR) = 1.02; 95% CI = 0.82–1.25; $P = .88$), and major arrhythmias (RR = 0.56; 95% CI = 0.26–1.19; $P = .13$).

Conclusion: Propofol sedation is able to reduce recovery time and shows similar safety compared with midazolam sedation during bronchoscopy.

Abbreviations: BIS = bispectral index, CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference, SpO_2 = oxyhemoglobin saturation.

Keywords: bronchoscopy, meta-analysis, midazolam, propofol, randomized controlled trials

1. Introduction

Bronchoscopy can cause various procedure-related symptoms and discomfort [1–3] and midazolam and an opioid is the most common combination used to improve patient tolerance and satisfaction.[4–6] Incremental midazolam sedation is recommended for patients undergoing bronchoscopy, and a bolus of midazolam is often administered when suffering from procedure-related discomfort during bronchoscopic procedures.[7–10] However, midazolam administration is limited by the delayed recovery.[11,12]

Various sedative protocols have been recently investigated for bronchoscopy. Intermittent propofol (2,6-diisopropylphenol) bolus has demonstrated good tolerance and fast recovery in patients undergoing bronchoscopy.[13–16] Propofol can reach peak concentration in a short time (2 minutes), and demonstrates fast redistribution and clearance so that it is available to maintain steady plasma concentrations with continuous infusion.[17–19] In addition, propofol is reported to provide a higher quality of sedation in terms of neuropsychometric recovery and patient tolerance during bronchoscopy than midazolam.[13]

However, propofol and opioids combination may result in oversedation and cardiopulmonary depression.[20,21] Considering these inconsistent effects, we therefore conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare the effectiveness of propofol versus midazolam in patients undergoing bronchoscopy.

2. Materials and methods

Preferred Reporting Items for Systematic Reviews and Meta-analysis statement[22] and the Cochrane Handbook for Systematic Reviews of Interventions[23] are used to guide the performance of this systematic review and meta-analysis. Two investigators have independently searched articles, extracted data, and assessed the quality of included studies.

2.1. Literature search and selection criteria

Several databases, including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library, are systematically searched using the keywords propofol, and midazolam, and bronchoscopy. The time in publishing the studies is from inception to October 28, 2017. The inclusion criteria are as follows: study design is RCT, study population are patients undergoing

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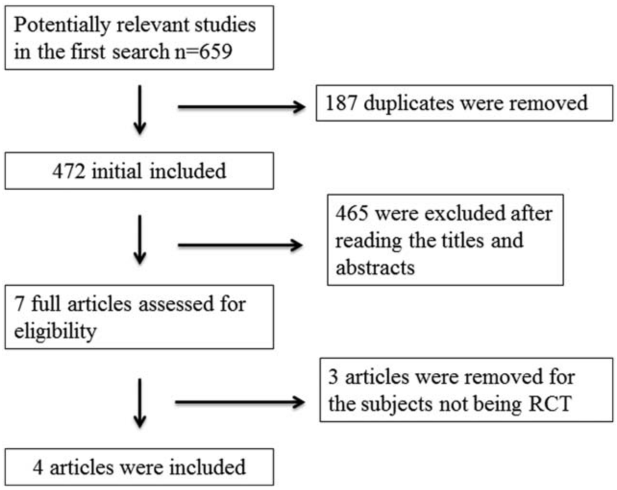

Figure 1. Flow diagram of study searching and selection process.

bronchoscopy, and intervention treatments are propofol versus midazolam.

2.2. Data extraction and outcome measures

Some information is collected for summarizing the baseline characteristics of patients in the included RCTs, and they include first author, publication year, sample size, baseline characteristics of patients, propofol, and midazolam. The primary outcome is recovery time. Secondary outcomes include operation time, induction time, lowest oxyhemoglobin saturation (SpO_2), SpO_2 <90%, and major arrhythmias.

2.3. Quality assessment in individual studies

The methodological quality of included RCTs is evaluated using the Jadad Scale, which is composed of 3 evaluation elements, including randomization (0–2 points), blinding (0–2 points), dropouts, and withdrawals (0–1 points).[24] One point would be allocated to each element on the basis of the description, randomization, and/or blinding of the included RCTs. The score of Jadad Scale has a range from 0 to 5 points, and 1 study with Jadad score ≥3 is thought to have the high quality.[25]

2.4. Statistical analysis

Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) is used for the all statistical analyses. We have calculated the SMD with 95% confidence interval (95% CI) for continuous outcomes (recovery time, operation time, induction time, and lowest SpO_2), and RR with 95% CIs for dichotomous outcomes (SpO_2 <90% and major arrhythmias). Heterogeneity is quantified with the I^2 statistic, and an I^2 value greater than 50% represents the significant heterogeneity. The random-effect model with DerSimonian and Laird weights is applied for all the meta-analyses regardless of the heterogeneity. When the significant heterogeneity presents, sensitivity analysis is conducted to detect the influence of a single study on the overall estimate or perform the subgroup analysis. Publication bias is not evaluated because of the limited number (<10). $P<.05$ is thought to be statistically significant.

3. Results

3.1. Literature search, study characteristics, and quality assessment

Figure 1 demonstrates the flow chart for the selection process and detailed identification. Six hundred fifty-nine publications are searched after the initial search of databases. One hundred eighty-seven duplicates and 465 papers after checking the titles/abstracts are excluded. Three studies are removed because of the study design and 4 RCTs are ultimately included in the meta-analysis.[13,26–28]

Table 1 summarizes the baseline characteristics of 4 eligible RCTs. [6,16,23,28] The 4 studies are published between 1993 and 2011, and the total sample size is 715. The detail methods of

Table 1

Characteristics of included studies.

		Propofol group						Midazolam group						
No.	Ref.	Number	Age, y	Male (No.)	Weight, kg	ASA score < 3	Methods	Number	Age, y	Male (No.)	Weight, kg	ASA score < 3	Methods	Jada scores
1	Lo et al[28]	243	59.9±13.1	145	61.1±11.3	145	Induction was performed using alfentanil (1:10 dilution, 4–5 μg/kg bolus) following an initial administration of 0.5 mg/kg intravenous propofol bolus. The dose of propofol was then carefully titrated by administering 10–20 mg boluses until the BIS index reached 70, and then propofol infusion (3–12 mg/kg/h).	249	61.9±14.7	139	59.9±11.4	130	Induction was performed using alfentanil (4–5 μg/kg bolus) following a 2 mg midazolam bolus, and maintenance with 1 mg/min midazolam boluses.	4
2	Clark et al[23]	43	57.9±11.4	27	74.9±15.6	40	Injecting a 4-mL drug bolus (40 mg of propofol), supplemental doses of drugs (20 mg of propofol) at an interval of ≥2 min to achieve and maintain BIS index between 70 and 85.	39	55.2±14.3	28	71.6±12.4	35	Injecting a 4-mL drug bolus (2 mg of midazolam), supplemental doses of drugs (2 mg of midazolam) at an interval of ≥2 min to achieve and maintain BIS index between 70 and 85.	4
3	Ozturk et al[6]	50	53.1±16.3	27	—	—	An initial bolus of propofol (1 mg/kg) intravenously followed by an infusion of 1 mg/kg/h, and supplemental dose of 10–20 mg of propofol to maintain.	50	49.1±16.7	28	—	—	2 mg midazolam intravenously as an initial bolus, followed by 1 mg at intervals of 2 min, and supplemental dose of 0.5–1 mg of midazolam to maintain.	4
4	Clarkson et al[16]	21	49.4,18.6±5.0	—	74.9,14.4±18.99	19	An initial bolus of propofol 60–80 mg/min up to 2 mg/kg followed by an infusion of 5–10 mg/kg/h.	20	51.2±16.8	—	75.1±14.3	15	An initial bolus of 2 mg midazolam over 30 s and supplementation after 2 min by 1 mg aliquots	3

ASA = American Society of Anesthesiologists, BIS = bispectral index.

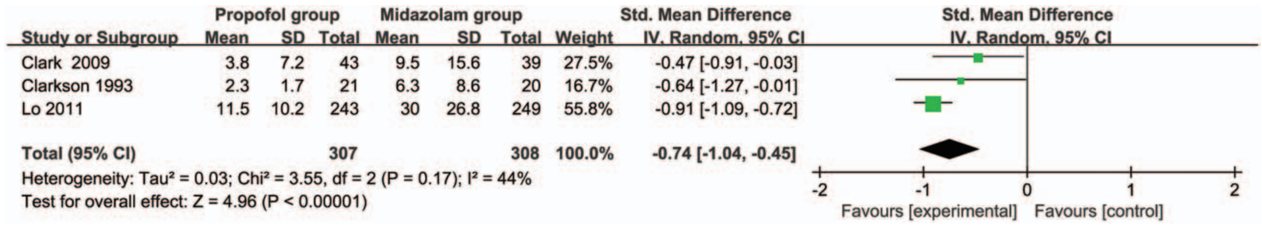

Figure 2. Forest plot for the meta-analysis of recovery time (min).

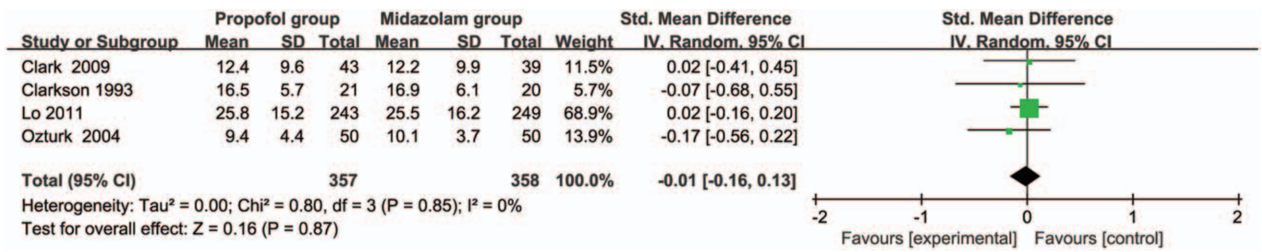

Figure 3. Forest plot for the meta-analysis of operation time (min).

propofol and midazolam for bronchoscopy are summarized in Table 1. Among the 4 RCTs, 3 studies report the recovery time,[13,26,27] 4 studies report the operation time,[13,26,27,28] 3 studies report the induction time,[13,26,27] 2 studies report the lowest SpO_2,[26,28] 3 studies report the SpO2 < 90%,[26–28] and 2 studies report the major arhythmias.[26,28] Jadad scores of the 4 eligible studies vary from 3 to 4, and thus, this quality assessment confirms these studies with high quality.

3.2. Primary outcome: recovery time

The random-effect model is used for the analysis of recovery time, and 3 included RCTs report this index. Propofol intervention results in a significantly shorter recovery time (SMD = −0.74; 95% CI = −1.04 to −0.45; P < .00001) than midazolam intervention for bronchoscopy, with low heterogeneity among the studies (I^2 = 44%, heterogeneity P = .17, Fig. 2).

3.3. Sensitivity analysis

The meta-analysis of recovery time has the low heterogeneity among the included studies, and thus, we do not perform sensitivity analysis by omitting 1 study in each turn or conduct the subgroup analysis.

3.4. Secondary outcomes

Compared with midazolam intervention for bronchoscopy, propofol intervention shows no remarkable influence on operation time (SMD = -0.01; 95% CI = -0.16 to 0.13; P = .87; Fig. 3), induction time (SMD = -0.58; 95% CI = -1.19 to 0.03; P = .06; Fig. 4), lowest SpO_2 (SMD = 0.24; 95% CI = -0.09 to 0.58; P = .15; Fig. 5), SpO_2 < 90% (RR = 1.02; 95% CI = 0.82–1.25; P = .88; Fig. 6), and major arrhythmias (RR = 0.56; 95% CI = 0.26–1.19; P = .13; Fig. 7).

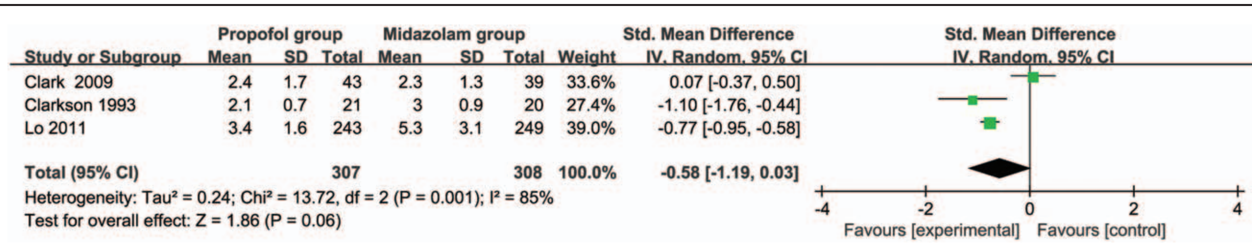

Figure 4. Forest plot for the meta-analysis of induction time (min).

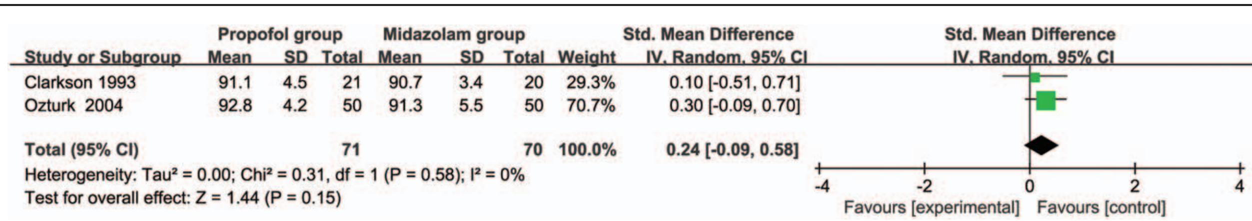

Figure 5. Forest plot for the meta-analysis of lowest SpO2 (%).

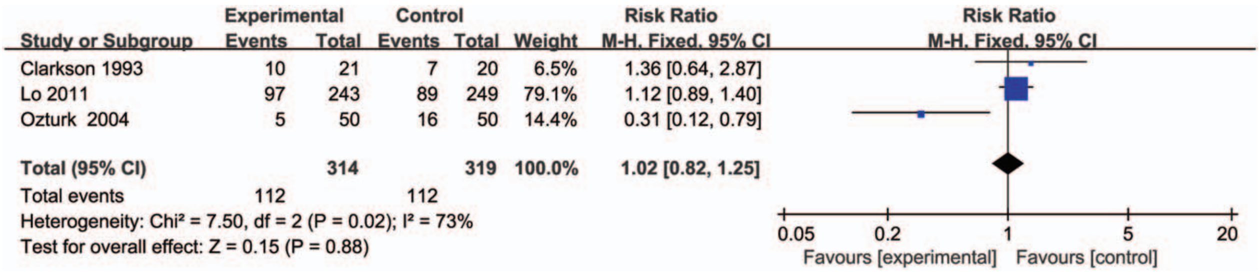

Figure 6. Forest plot for the meta-analysis of $SpO_2 < 90\%$.

Figure 7. Forest plot for the meta-analysis of major arrhythmias.

4. Discussion

Propofol sedation is reported to provide faster induction, less procedural interference for bronchoscopists, better tolerance, and faster recovery for patients undergoing bronchoscopy than midazolam infusion.[27,29] Our meta-analysis suggests that compared with midazolam infusion during bronchoscopy, propofol sedation treatment can substantially decrease recovery time, but has no significant influence on the operation time and induction time.

Bispectral index (BIS) is known as a noninvasive and objective indicator of the depth of anesthesia. Good correlations are revealed between propofol drug concentration, sedative score, and BIS level.[30,31] BIS index between 70 and 85 can be maintained via BIS-guided propofol bolus during simple bronchoscopy procedures.[13] BIS level of 65 to 75 is recommended for bronchoscopy sedation, and a BIS level of 70 is set for induction in this protocol to achieve patients who are amnesic but still with reflex responsiveness to noxious stimulation.[30,32]

Patients receiving propofol in bronchoscopy show better global tolerance, but have no influence on the perception of coughing, bronchoscopists' assessment compared with patients using midazolam.[13] The discomfort score and safety profiles of patients with propofol are similar to those with midazolam sedation.[16] One included RCT has reported that BIS-guided propofol infusion is as safe as the current standard method of clinically judged midazolam sedation based on the number of patients experiencing hypoxemia and hypotension.[27]

Patients with propofol sedation demonstrate similar lowest SpO_2, the number of $SpO_2 < 90\%$, and major arrhythmias compared with midazolam infusion during bronchoscopy based on the results of our meta-analysis. BIS-guided propofol infusion with alfentanil administration is revealed to provide additional benefits for the bronchoscopists (less procedural interference) and patients (less discomfort from scope insertion, dyspnea, and cough), and these may be explained by that adding alfentanil can modify the pharmacokinetic property of propofol and provide a more steady plasma concentration in order to reduce the required dose of propofol and recovery time with less cardiovascular depression.[17,33,34]

There are still several limitations. First, only 4 RCTs are included in this meta-analysis, and 2 of them have a relatively small sample size ($n < 100$). These may lead to overestimation of the treatment effect in smaller trials. Although there is low heterogeneity among the included studies, different methods of propofol and midazolam in each included RCT may affect the pooled results. Finally, the plasma concentration of drug is not tested in the included RCT. The optimal dose and method of esmolol treatment remains elusive.

5. Conclusion

Propofol sedation can provide the shorter recovery time during bronchoscopy than midazolam sedation. Propofol sedation is recommended to be administered for bronchoscopy with caution, and more studies are needed to confirm this issue.

Author contributions

Conceptualization: Tianyang Dai.
Data curation: Zhizhen Wang.
Methodology: Zhizhen Wang, Tianyang Dai.
Visualization: Zhi Hu.
Writing – original draft: Zhi Hu.
Writing – review & editing: Zhi Hu.

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