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Review Article

Comparison of nebulized versus standard lidocaine during bronchoscopy: a meta-analysis of randomized controlled trials

Yan Li[1], Yanqiong Lou[1], Anqiang Han[1], Ying Han[2]

[1]*Department of Respiratory, Internal Medical Ward, Ningbo No. 6 Hospital, Ningbo 315040, Zhejiang, China;*
[2]*Department of Anesthesiology, Ningbo No. 6 Hospital, Ningbo 315040, Zhejiang, China*

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Abstract: Introduction: The comparive efficacy of nebulized versus standard lidocaine during bronchoscopy remains controversial. In this study, systematic review and meta-analysis were conducted to explore the influence of nebulized versus standard lidocaine for patients undergoing bronchoscopy. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were searched through October 2018 for randomized controlled trials (RCTs) assessing the effect of nebulized versus standard lidocaine for bronchoscopy. This meta-analysis was performed using the random-effect model. Results: Five RCTs involving 214 patients are included in the meta-analysis. Overall, compared with standard lidocaine for bronchoscopy, nebulized lidocaine was associated with substantially reduced dose of lidocaine (Std. MD=-1.11; 95% CI=-2.15 to -0.08; P=0.04) and duration of the procedure (Std. MD=-0.42; 95% CI=-0.76 to -0.09; P=0.01), as well as increased Sp02 (Std. MD=0.61; 95% CI=0.19 to 1.04; P=0.0005), but showed no obvious effect on fentanyl requirement (RR=0.70; 95% CI=0.43 to 1.13; P=0.14), Pa02 (Std. MD=0; 95% CI=-0.42 to 0.42; P=1.00), heart rate (Std. MD=-0.15; 95% CI=-0.78 to 0.47; P=0.63), SBP (Std. MD=-0.08; 95% CI=-0.49 to 0.34; P=0.72), DBP (Std. MD=-0.13; 95% CI=-0.54 to 0.29; P=0.55), and adverse events (RR=0.49; 95% CI=0.19 to 1.25; P=0.13). Conclusions: Nebulized lidocaine exhibited positive influence on the dose of lidocaine, and mean duration of the procedure in relative to standard lidocaine during bronchoscopy.

Keywords: Nebulized lidocaine, standard lidocaine, bronchoscopy, randomized controlled trials, meta-analysis

Introduction

Bronchoscopy is widely accepted as the essential approach for the diagnostic work-up and management of patients with various acute or chronic pulmonary diseases [1-3]. Sufficient sedation is essential to increase patient comfort and tolerance [4, 5]. Different drugs have been developed for sedation, but there is no gold standard sedation [6]. The combination of the short-acting benzodiazepine midazolam with opiates or propofol is generally used and proves to be effective and safe [5, 7, 8].

In order to reduce coughing and the dosage of sedative drugs, local anesthetics such as lidocaine are administered topically to the upper airways and the tracheobronchial tree through the working channel of bronchoscope [9-11]. It is difficult to achieve even distribution of lidocaine in the bronchial system and complete anaesthesia of the airway walls through the delivery using a syringe. Spray catheters such as the Enk Fiberoptic Atomizer Set® is designed to promote the nebulization of lidocaine during the bronchoscopy procedure using a constant oxygen flow [12]. This device used for diagnostic bronchoscopies is found to be safe and effective. Lidocaine administration via nebulizer during bronchoscopy exhibits reduced consumption of lidocaine and fentanyl compared with conventional administration via syringe [13, 14].

However, the efficacy of nebulized lidocaine versus standard lidocaine during bronchoscopy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [6, 12, 14, 15]. With accumulating evidence, a systematic

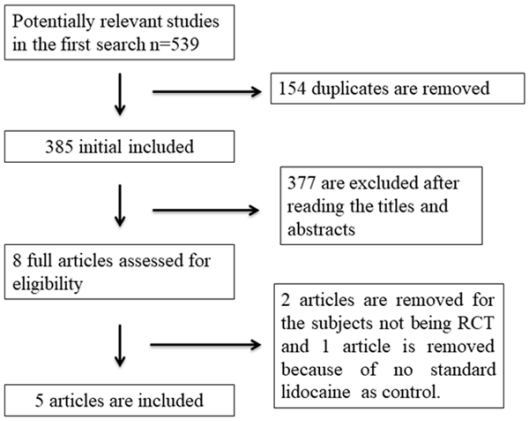

Figure 1. Flow diagram of study search and selection process.

review and meta-analysis of RCTs was performed here to compare their efficacy 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 are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16].

Search strategy and study selection

Two investigators 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: nebulized lidocaine, and bronchoscopy. Reference lists of the screened full-text studies were also checked to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients undergoing bronchoscopy; (ii) intervention: nebulized lidocaine; (iii) comparison: standard lidocaine; (iv) study design: RCT.

Data extraction and outcome measures

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

The primary outcome is the dose of lidocaine. Secondary outcomes include mean duration of the procedure, fentanyl requirement, SpO2, PaO2, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and adverse events.

Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [17]. 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 [18].

Statistical analysis

The standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (the dose of lidocaine, mean duration of the procedure, SpO2, PaO2, heart rate, SBP, and DBP) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (fentanyl requirement, and adverse events) were estimated. A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2>50\%$ indicates significant heterogeneity [19]. 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 were 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 is shown in **Figure 1**. 539 potentially relevant articles are identified initially. Finally, five RCTs that meet our inclusion criteria are included in the meta-analysis [6, 12, 14, 15, 20].

Table 1. Characteristics of included studies

NO	Author	Nebulized lidocaine group						Standard lidocaine group						Jada scores
		Number	Age (years)	Male (n)	Body weight (kg) or body mass index (kg/m^2)	Smoking history (pack-years)	Methods	Number	Age (years)	Male (n)	Body weight (kg) or body mass index (kg/m^2)	Smoking history (pack-years)	Methods	
1	Muller 2018	30	67.9±9.08	21	86.64±15.81 kg	5 (0-30), median (interquartile range)	endobronchial lidocaine via nebulizer	30	64.47±11.56	18	79.33±16.5 kg	5 (0-30), median (interquartile range)	endobronchial lidocaine via syringe	4
2	Dreher 2016	15	62.8±11.7	4	73.7±13.49 kg	16.4±19.60	nebulized lidocaine	15	69.0±6.7	4	72.0±13.35 kg	27.4±24.09	conventional lidocaine by injection	5
3	MacDougall 2011	25	-	-	-	-	nebulized lidocaine through an Enk device	25	-	-	-	-	conventional injection of lidocaine	3
4	Lee 2011	20	67.9	12	28.2 kg/m^2	-	nebulized lidocaine	20	64.3	8	27.8 kg/m^2	-	standard lidocaine by injection	4
5	Graham 1992	16	-	-	-	-	lidocaine delivered by nebulizer	18	49.7	-	1	-	standard lidocaine by injection	3

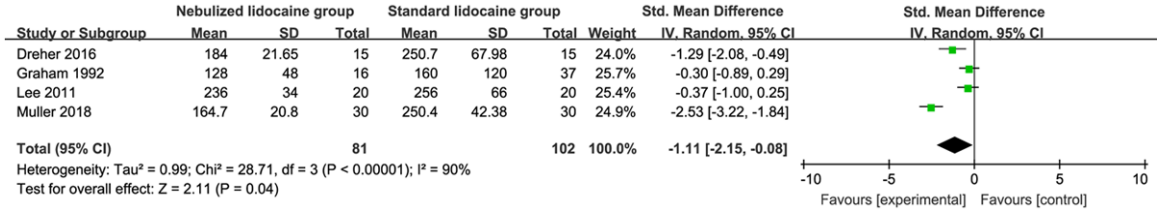

Figure 2. Forest plot for meta-analysis of the dose of lidocaine.

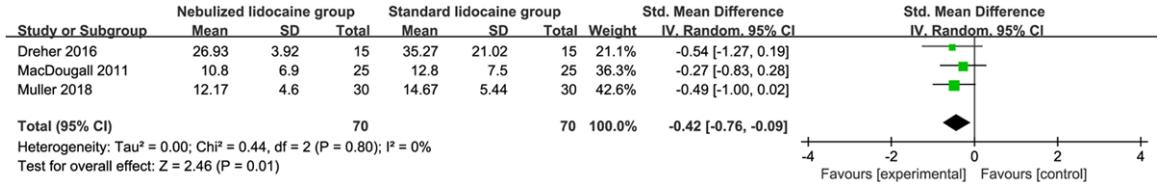

Figure 3. Forest plot for meta-analysis of mean duration of the procedure.

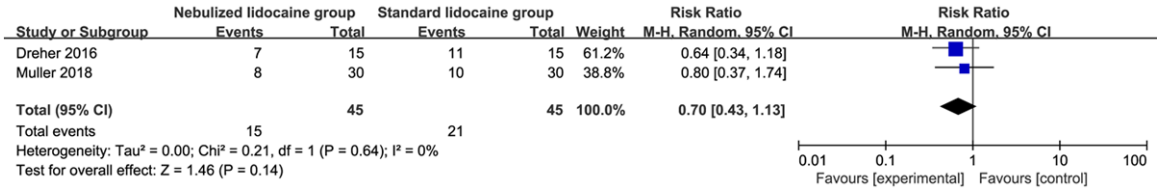

Figure 4. Forest plot for meta-analysis of fentanyl requirement.

The baseline characteristics of the five eligible RCTs in the meta-analysis are summarized in **Table 1**. The five studies were published between 1992 and 2018, and sample sizes range from 30 to 60 with a total of 214. The intervention treatments are nebulized lidocaine versus standard lidocaine by injection.

Among the five studies included here, four studies report the dose of lidocaine [6, 14, 15, 20], three studies report mean duration of the procedure [6, 12, 14], two studies report fentanyl requirement, SpO2, PaO2, heart rate, SBP and DBP [6, 14], three studies report adverse events [6, 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: the dose of lidocaine

This outcome data was analyzed with the random-effects model, and compared to standard lidocaine for bronchoscopy, nebulized lidocaine results in significantly reduced dose of lidocaine (Std. MD=-1.11; 95% CI=-2.15 to -0.08; P=0.04), with significant heterogeneity among the studies (I^2=90%, heterogeneity P<0.00001) (**Figure 2**).

Sensitivity analysis

Significant heterogeneity was observed among the included studies for the primary outcomes, but there was still remarkable heterogeneity when performing sensitivity analysis via omitting one study in turn.

Secondary outcomes

In comparison with standard lidocaine for bronchoscopy, nebulized lidocaine is associated with markedly reduced duration of the procedure (Std. MD=-0.42; 95% CI=-0.76 to -0.09; P=0.01; **Figure 3**), but showed no obvious impact on fentanyl requirement (RR=0.70; 95% CI=0.43 to 1.13; P=0.14; **Figure 4**). In addition, nebulized lidocaine exhibits the significant increase in SpO2 than that in standard lidocaine (Std. MD=0.61; 95% CI=0.19 to 1.04; P=0.0005; **Figure 5**), but exerted no substantial impact on PaO2 (Std. MD=0; 95% CI=-0.42 to 0.42; P=1.00; **Figure 6**), heart rate (Std.

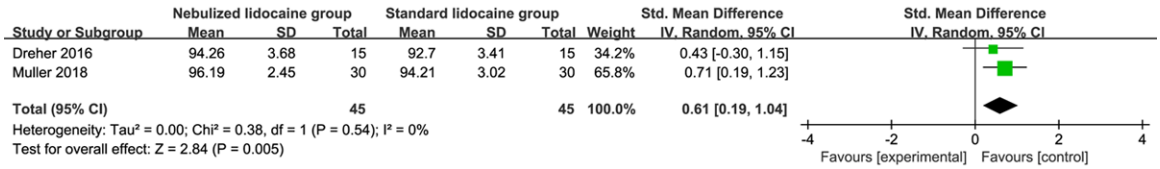

Figure 5. Forest plot for meta-analysis of SpO2 (%).

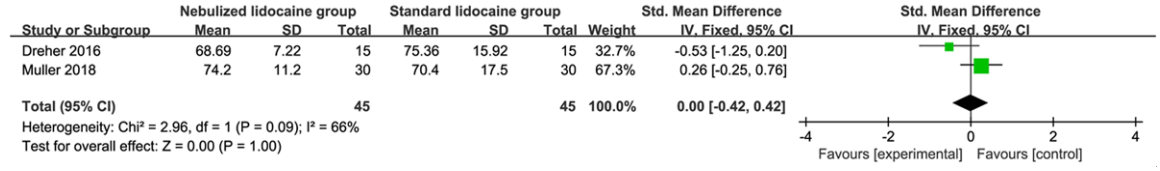

Figure 6. Forest plot for meta-analysis of PaO2.

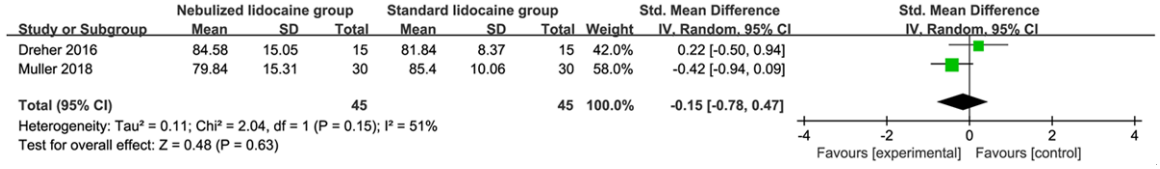

Figure 7. Forest plot for meta-analysis of heart rate (beats/min).

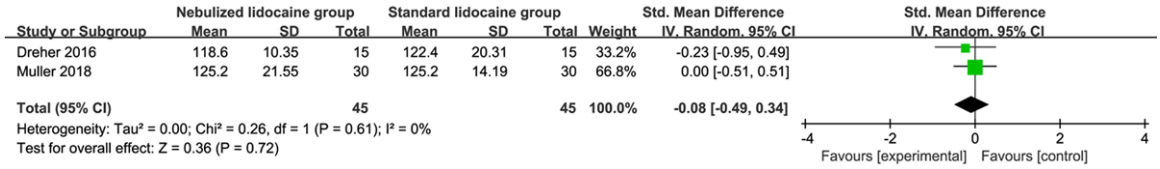

Figure 8. Forest plot for meta-analysis of SBP (mmHg).

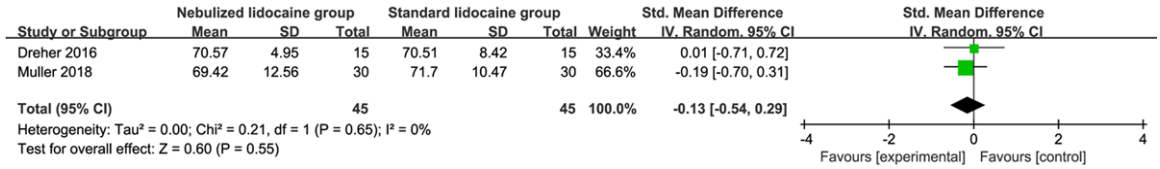

Figure 9. Forest plot for meta-analysis of DBP (mmHg).

MD=-0.15; 95% CI=-0.78 to 0.47; P=0.63; **Figure 7**), SBP (Std. MD=-0.08; 95% CI=-0.49 to 0.34; P=0.72; **Figure 8**), DBP (Std. MD= -0.13; 95% CI=-0.54 to 0.29; P=0.55; **Figure 9**), and adverse events (RR=0.49; 95% CI=0.19 to 1.25; P=0.13; **Figure 10**).

Discussion

Bronchoscopy should be performed under sedation to facilitate the procedure and increase patient tolerance, comfort, and cooperation [21-24]. Combination sedation using two or even three different drugs is revealed to be safe and may have several advantages over sedation with one drug [25-27]. For instance, nebulizer lidocaine in comparison with midazolam and propofol is applied for the sedation of bronchoscopy, and the results confirm the safety and important efficacy. In addition, nebulizer lidocaine is associated with less fentanyl consumption and cough suppression [14]. Topical

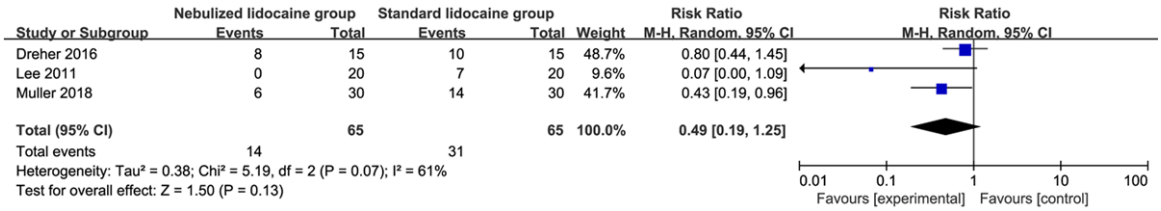

Figure 10. Forest plot for the meta-analysis of adverse events.

use of lidocaine during flexible bronchoscopy is generally accepted and recommended by current guidelines [4, 6].

However, endobronchial lidocaine may lead to some side effects such as cardiac arrhythmias, seizures or deterioration in pulmonary function [28, 29]. The dosage of lidocaine should be used as low as possible to reduce the risk of side effects. In some studies, lidocaine delivery via nebulizer during diagnostic fiberoptic bronchoscopy needs significantly reduced dosage without increasing the dosage of other sedative drugs compared to conventional delivery [6, 14]. The meta-analysis suggests that compared to standard lidocaine for bronchoscopy, nebulized lidocaine has positive impact on the decrease in the dose of lidocaine and the mean duration of the procedure, but shows no significant effect on the number of fentanyl requirement.

In one RCT for bronchoscopy, lidocaine use via nebulizer results in higher SpO2, and lower supplemental oxygen flow rate needed to maintain SpO2>95% than that in standard use of lidocaine. Arterial post-interventional PaO2 after using nebulizer lidocaine significantly increases compared to pre-interventional PaO2 [6]. In meta-analysis, higher SpO2 was also found after lidocaine use via nebulizer than standard use through syringe for bronchoscopy. There was no statistical difference of PaO2, heart rate, SBP and DBP between two groups. The safety of nebulized lidocaine is also confirmed in our results, as evidenced by no significant difference of adverse events between two groups. In addition, lidocaine administered via nebulizer may lead to better cough suppression compared with lidocaine administered via syringe [30, 31]. Regarding sensitivity analysis, significant heterogeneity is still observed when conducting the meta-analysis via omitting one study in turn. This heterogeneity may be caused by different diffusion and locations of lidocaine, the time span between lidocaine administration and the passage of the bronchoscopy etc.

This meta-analysis also has several potential limitations. First, the analysis is based on five RCTs, and all 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 explore this issue. Next, there is significant heterogeneity when performing the sensitivity analysis, and may be caused by the difference in diffusion and locations of lidocaine, the time span between lidocaine administration and the passage of the bronchoscopy etc. Finally, some unpublished and missing data may lead to some bias for the pooled effect.

Conclusion

Nebulized lidocaine can provide additional benefits for bronchoscopy.

Disclosure of conflict of interest

None.

Address correspondence to: Ying Han, Department of Anesthesiology, Ningbo No. 6 Hospital, Ningbo 315040, Zhejiang, China. Tel: +86-17783008788; E-mail: hanyinghanying@163.com

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