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Nebulized Ipratropium bromide protects against tracheal and bronchial secretion during bronchoscopy

A randomized controlled trial

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Abstract

Background: Anticholinergic administration prior to flexible bronchoscopy has been investigated, but studies have not yielded consistent results.

Methods: Patients were randomized 1:1 to receive nebulized 4 ml ipratropium bromide (1 mg, n = 125) or placebo (n = 125) for 15 minutes as premedication, 20 to 40 minutes before bronchoscopy. Airway secretions, bleeding, patient discomfort, procedure time, and procedure-related adverse events were compared between the groups.

Results: Nebulized ipratropium bromide prior to bronchoscopy could reduce airway secretions and patient discomfort ($P = .02$; $P < .001$, respectively), but not tracheobronchial bleeding or procedure time ($P = .51$, $P = .36$, respectively). Chest nodule or mass was the most common indication for performing bronchoscopy. The adverse events were higher in ipratropium bromide group, and hypertension was the most common complication.

Conclusion: Nebulized ipratropium bromide prior to bronchoscopy is a more effective regimen that shows a practical benefit on the airway secretions and patient comfort, though these effects may not translate into any marked reduction in bleeding or of procedure time under general anesthesia. We suggest that routine nebulized ipratropium bromide premedication for bronchoscopy could be useful and beneficial.

Trial Registration: chictr.org.cn: ChiCTR1800016881.

Abbreviations: BP = blood pressure, TBNA = transbronchial needle aspiration.

Keywords: bronchoscopy, ipratropium bromide, randomized controlled trial, secretion

1. Introduction

Flexible bronchoscopy was introduced into pulmonology 50 years ago.[1] With the development of some technological advances, it has become an invaluable diagnostic tool for many lung disorders and is a safe procedure with low (0.1–2.5%) morbidity and very low (0.05%) mortality.[2] However, the hypersecretion in the trachea and bronchi during general anesthesia makes it hard for bronchoscopist to observe and

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FW, HZ, YZ, and HZ contributed equally to this work and shared the first authorship.

Proposals should be directed to fengmingluo@outlook.com. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third-party website chictr.org.cn.

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perform their duties. M3 muscarinic acetylcholine receptors are mainly located in respiratory smooth muscle, submucosal glands, goblet cells, airway epithelial cells, and vascular endothelial cells. The M3 receptor can increase glandular secretions, which is important in the parasympathetic-mediated digestion response as well as in bronchial secretions.[3] Antagonizing M3 receptors can inhibit mucus hypersecretion.

Mucous hypersecretion during bronchoscopy is an issue for bronchoscopists because it makes the procedure difficult to perform and increases the procedure time. Anticholinergic agents are effective bronchodilators and are used as a premedication to reduce bronchial secretions.[4–8] For example, atropine is the most frequently used premedication but it may lead to arrhythmias or urinary retention, particularly when injected intramuscularly.[9] Glycopyrrolate appears to have certain advantages over atropine for patients undergoing bronchoscopy.[10,11] Ipratropium bromide is a synthetic analog of atropine which has a wider therapeutic margin when given by inhalation compared to atropine.[12]

Previous studies have yielded conflicting results regarding the anticholinergic effectiveness of those agents during bronchoscopy. Some studies have shown significantly less secretion when glycopyrrolate is administered,[10,11] while others noted no substantial benefit.[13–17] However, just one study compared ipratropium bromide with atropine. The results showed that inhaled ipratropium bromide protects against the deleterious effects of bronchoscopy on pulmonary function caused by topical lidocaine anesthesia, whereas intramuscular atropine does not.[9] The protective ability of ipratropium against airway secretions during bronchoscopy had not been previously evaluated. As atropine premedication before bronchoscopy has side effects, we tried to find other anticholinergic drugs to lower the incidence of adverse events and improve the specific effects in the lung. Therefore, we gave patients nebulization of ipratropium bromide prior to the bronchoscopy procedure to investigate whether ipratropium bromide premedication influences airway secretions, patient discomfort, and procedure time.

2. Materials and methods

2.1. Trial design

In this randomized, double-blind, placebo-controlled study, patients were randomized 1:1 to receive nebulized 4 ml ipratropium bromide (1 mg, n = 125) or placebo (n = 125) for 15 minutes as premedication, 20 to 40 minutes before bronchoscopy. The study was conducted in compliance with the ethics principles expressed in the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The study protocol was approved by the institutional review boards of West China Hospital, Sichuan University (China, Chengdu). During the study, the investigators, bronchoscopist and participants were masked to the type of premedication.

2.2. Patients

Written informed consent was obtained from all patients. A total of 250 patients undergoing fiberoptic bronchoscopy participated in this randomized, placebo-controlled, double-blind study from June 2018 to December 2018 (chictr.org.cn, Identifier: ChiCTR1800016881). All the inpatients and outpatients older than 18 years and undergoing fiberoptic bronchoscopy under general anesthesia were eligible. Patients were excluded if they were any of the following: afflicted with glaucoma or urinary retention, allergic to ipratropium bromide, pregnant or lactating, intubated prior to initiation of the procedure, had received prior head and neck irradiation, undergoing brachytherapy or therapeutic bronchoscopy, scheduled to undergo or undergoing brachytherapy or therapeutic bronchoscopy, had previously participated in a similar study, or unable to provide informed consent. Patients were randomized according to the procedure provided by SPSS software (IBM SPSS, version 22, Chicago, IL), which generates random deviates from the uniform distribution on the interval (1, 2).

2.3. Procedure

All patients were instructed not to eat or drink for at least six hours before the procedure and were randomly assigned to receive nebulized 4 ml (1 mg) ipratropium bromide or 4 ml saline for 15 minutes. The premedication was administered by investigators (FP Wang, H Zheng, YL Zhang) about 20 to 40 minutes before the procedure. Before the procedure, to achieve general anesthesia, patients also received an intravenous injection of sufentanil 0.1–0.15 μg/kg, propofol 1.5–2 mg/kg (or etomidate 0.3–0.4 mg/kg), and succinylcholine 1.5–2 mg/kg. Laryngeal mask airway with mechanical ventilation was used to all patients. Bronchoscopy was performed with a flexible bronchoscope (model BF-1TQ290; Olympus; Tokyo, Japan) with the patient in the supine position. Approximately 5 mL of 2% lidocaine solution was instilled over the vocal cords prior to advancing the bronchoscope. The bronchoscopist (J Shi and Y Luo) performed the procedure. During bronchoscopy, all patients received supplemental oxygen. The oxygenation status, heart rate, and blood pressure (BP) were monitored throughout the procedure and the recovery period (iPM patient monitor, Shenzhen Mindray Bio-Medical Electronics Co., Ltd, China). Alarms were set to sound if the saturation went below 90% or if the heart rate went below 55 or above 130 beats-per-minute. Different biopsy techniques were utilized, depending on the location of the lesion.

2.4. Outcomes and safety assessment

During bronchoscopy, the larynx and tracheobronchial secretions was assessed by the operator (HZ). The evaluation method was performed according to Williams et al[18], and airway secretions were graded as follows:

1) almost none,
2) needing saline to wash out,
3) excessive, making it difficult to see. 5 ml aliquots of saline used to wash the airway were recorded.

Tracheobronchial bleeding was also graded as described before:

1) no saline washing required to clear,
2) requiring saline to wash,
3) requiring instillation of epinephrine (1 mg in 20 ml of saline).[18]

A subjective assessment of patient comfort was also made after the procedure, grading as

1) satisfied, feeling nothing,

2) a little uncomfortable but tolerable,
3) too uncomfortable to tolerate.

The procedural time was noted with a stopwatch timing from the first introduction to the complete withdrawal of the bronchoscope. Forceps biopsy, bronchial brushing, bronchoalveolar lavage, bronchial washings, and transbronchial needle aspiration (TBNA) were performed based on the varied airway lesions. Patient comfort was evaluated after the patient recovered from the anesthesia

Adverse events throughout the entire procedure were monitored. Heart rates lower than 55 beats/min during bronchoscopy or a decrease in heart rate of ≥15 beats/min from pre-procedure value were considered bradycardia. Hypotension was defined as a decrease in systolic BP ≥20 mmHg or a decrease in diastolic BP ≥10 mmHg from the pre-procedure recordings.

2.5. Statistical analysis

Power calculation regarding the airway secretion was conducted and showed that a sample size of 75 completed participants per group provides > 80% statistical power for a paired-sample *t* test with 0.05 set as α (alpha) for Type I error. Allowing for expected attrition, recruitment of 250 participants was planned. Data were presented as mean ± SD or as a count (percentage). Comparison between two groups was performed by using a *t* test, Mann–Whitney *U* test or Chi-squared–test. The primary endpoint is airway secretions, secondary endpoints are procedure time, bleeding grade, complications, and overall patient comfort. The Mann–Whitney *U* test was used for airway secretions, bleeding grade and patient comfort. A *t* test was used for procedure time. Significance was defined as $P < .05$. Statistical analyses were performed using SPSS software (IBM SPSS, version 22, Chicago, IL).

3. Results

Fig. 1 summarizes the study selection process. In total, 250 patients were included, 125 received ipratropium bromide and 125 received placebo. The demographic characteristics of the patients are presented in Table 1. The two groups of patients did not differ significantly in terms of age, sex, and history of smoking.

Table 2 showed the indications, bronchoscopy findings and procedures performed during bronchoscopy. Chest nodule or mass was the most common indication for performing bronchoscopy, and cough is the secondary reason. 11 patients of the ipratropium bromide group and 17 patients of placebo group required therapeutic bronchoscopy. Only one patient in the placebo group received sputum suction. Table 3 shows the outcomes. In both groups, most patients were rated grade 1 in terms of airway secretion and only needed one aliquot of saline. In the placebo group, more patients required saline to clear tracheobronchial secretions. No patients, in either of the two groups, had excessive secretions that made the procedure difficult or used more than two aliquots of saline. In both groups a large population of patients did not need saline to wash tracheobronchial bleeding. Ipratropium bromide significantly decreased the airway secretion and improved the patients comfort ($P = .02$,

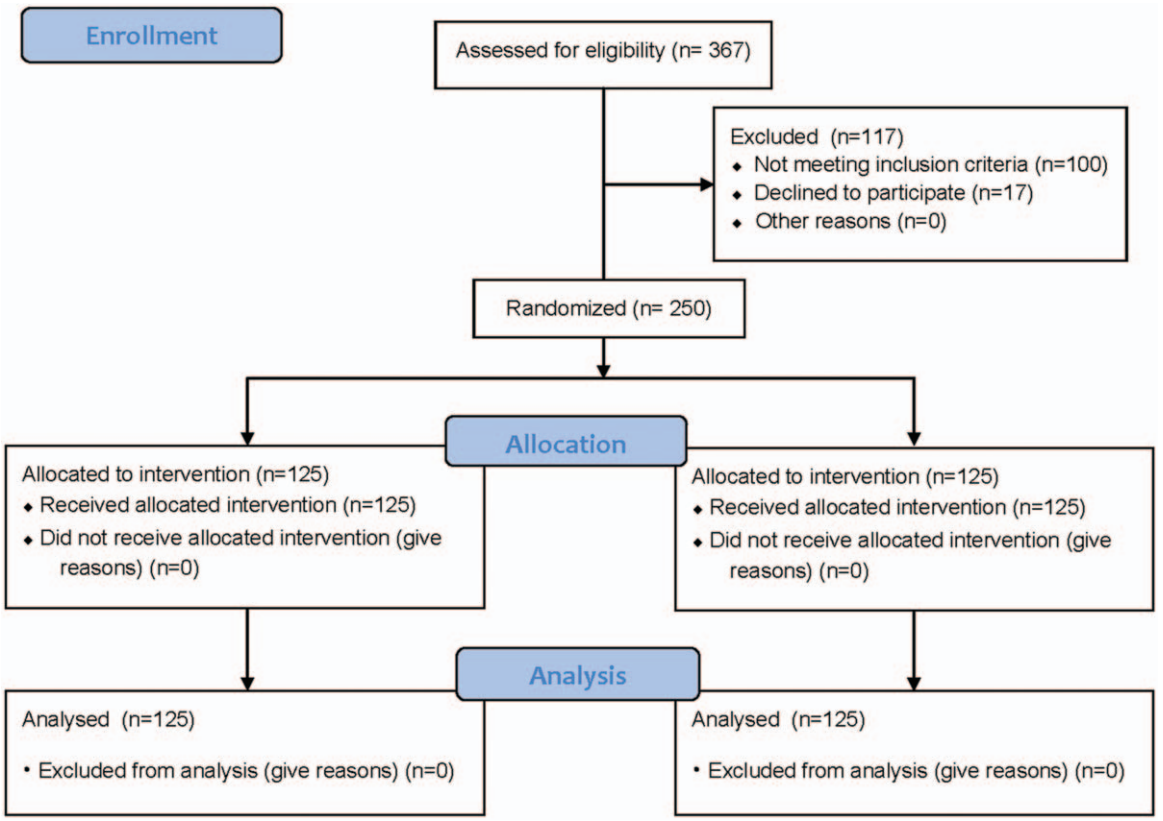

Figure 1. Enrollment flow diagram.

Table 1

Demographic characteristics of patients.

Variables	Ipratropium bromide (n = 125)	Placebo (n = 125)
Age (mean, SD)	50.67 ± 11.54	49.65 ± 11.75
Male (N, %)	68 (55.40%)	65 (52.00%)
Smoking History (N, %)		
Never smoker	65 (52.00%)	64 (51.20%)
Former smoker	33 (26.40%)	37 (29.60%)
Current smoker	27 (21.60%)	24 (19.20%)
Biopsy specimen obtained	48 (38.40%)	50 (40.00%)

$P = .00$, respectively), while it had no effect on tracheobronchial bleeding compared to placebo ($P = .51$). However, more patients in the placebo group felt a little uncomfortable. Similarly, no significant differences were found in number of aliquots of saline used and procedure time ($P = .37$; $t = -0.927$, $P = .36$, 95% CI: -2.38 to 0.86, respectively). All bronchoscopies were performed successfully in all patients. 24% (30 of 125) and 20.8% (26 of 125) patients in each group had complications (Table 4). Hypertension was the most common complication. Only one patient in each group developed tachycardia. Bradycardias occurred in two patients in the ipratropium bromide group and one patient in the placebo group. Nearly half of the bronchoscopy findings in both groups were normal. More stenosis, endobronchial mass or nodule, and external compression was observed in the ipratropium bromide group.

Table 2

Summary of indications, bronchoscopy findings and procedures performed.

Variables	Ipratropium bromide (n = 125)	Placebo (n = 125)
Indications		
Chest nodule or mass	36	38
Cough	33	18
Pulmonary infiltrate	6	19
Hemoptysis	12	8
Previous cancer	14	8
Tuberculosis	5	7
Others	8	10
Findings		
Normal	56	64
Stenosis	18	10
Endo-bronchial mass/nodule	24	18
Bronchial stricture or obliteration	4	5
Secretion	7	10
Bleed	3	3
Mucosal injury (swelling,congestion,ulceration)	8	14
External compression	5	1
Procedures performed		
Inspection only	26	31
Biopsy	6	6
Biopsy/brush	26	24
Brushing	5	2
TTNA/brush	6	8
Biopsy/BAL	2	2
BAL	30	20
BAL/brush	16	19
BAL/brush/biopsy	8	10
Inspection prior to stent placement	0	2
Sputum suction	0	1
Therapy		
Airway stenosis	8	12
Foreign body	3	5

Table 3

Outcomes in Patients Undergoing Flexible Bronchoscopy.

Outcomes	Ipratropium bromide (n = 125)	Placebo (n = 125)	*P* value
Airway secretions			
Grade 1 (almost none)	100	84	.02*
Grade 2 (needing saline to clear)	25	41	
Grade 3 (excessive, difficult to see)	0	0	
Aliquots of saline used			
1	20	36	.37
2	3	4	
>2	2	1	
Tracheobronchial bleeding			
Grade 1 (No saline wash)	98	102	.51
Grade 2 (Saline used)	5	5	
Grade 3 (Adrenaline used)	22	18	
Patient comfort			
Grade 1 (satisfied)	106	52	.00*
Grade 2 (a little uncomfortable)	19	73	
Grade 3 (too uncomfortable to tolerate)	0	0	
Procedure time, min	11.40 ± 6.11	12.16 ± 6.83	.36

* $P < .05$.

4. Discussion

Our study proved that nebulized ipratropium bromide prior to bronchoscopy could reduce airway secretions and patient discomfort with higher complications (especially for hypertension), but not tracheobronchial bleeding or procedure time. To the best of our knowledge, this is the first study to investigate the safety and efficacy of nebulized ipratropium bromide premedication for bronchoscopy under general anesthesia.

Anticholinergic premedication has been widely used for fiberoptic bronchoscopy for many years because it not only can prevent vasovagal phenomena, reflex bronchoconstriction, and bradycardia, but also could help to decrease secretions in the pharynx and airways. Several studies have evaluated the effects of anticholinergic premedication for flexible bronchoscopy. Unfortunately, the results were controversial. Rees et al[19] first evaluated atropine premedication in 1983, they found that atropine did not show a significant difference regarding sedative effect, tolerance, or coughing. Three years later, Thorburn et al. showed improvement in pulmonary mechanics with both atropine and glycopyrrolate prior to instrumentation, but no improvement after fiberoptic bronchoscopy under general anesthesia.[20]

Table 4

Complications Recorded During Bronchoscopy.

Complications	Ipratropium bromide (n = 125)	Placebo (n = 125)
All events*	30 (24%)	26 (20.8)
Hypertension*	21 (16.8%)	18 (14.4%)
Hypotention	4 (3.2%)	4 (3.2%)
Desaturation	2 (1.6%)	2 (1.6%)
Tachycardia	1 (0.8%)	1 (0.8%)
Bradycardia	2 (1.6%)	1 (0.8%)

* $P < .05$.

In terms of airway secretion, Cowl et al[16] reported statistical significance only for patient scores but not significance for bronchoscopist scores and bronchoscopist rating of secretion among atropine, glycopyrrolate, and placebo. They concluded that anticholinergic agents prior to bronchoscopy gave no appreciable benefit from the resultant reduction in airway secretions under topical anesthesia. However, another study also compared atropine and glycopyrrolate under local anesthesia [17]; the study found that the bronchoscopist scores for airway secretions were significant while no extreme differences were found in patient-reported scores and discomfort. Williams et al. [18] also did not find differences in secretions in a comparison of atropine and placebo. Interestingly, our results proved that ipratropium bromide significantly reduced airway secretions and improved patient comfort in contrast to previous studies. We believe the main reasons may be:

1) we used a different anticholinergic premedication (ipratropium bromide) and different administration (nebulization), all the patients involved the prior studies were given drugs via intramuscular injection, and all the prior studies investigated the secretions comparing atropine, glycopyrrolate or both to control;
2) a difference of anesthesia while undergoing bronchoscopy (we assessed the patients under general anesthesia during the procedure while earlier studies evaluated the patients under topical anesthesia);
3) the different assessment method for airway secretions, our assessment of airway secretions was different from Malik et al. and Cowl et al. but the same as Williams et al. The previous two studies used a modified visual analog scale ranging from 0–100 mm (0 means the worst and 100 indicates the most favorable observation). Although this quantified the secretions, the results are extremely subjective and varied. Here in our study, we used a relatively objective grading instrument described by Williams et al. which gives us more confidence in our results.

Consistent with the previous studies, we did not see any differences in bleeding and procedure time. As coughing can be varied due to the disease and is difficult to test in a meaningful and objective way, we did not investigate it. For example, patients with a chief complaint of cough could cough more than others. Since the pulmonary function depends on the diagnosis; such as chronic obstructive pulmonary disease, interstitial lung disease, and smoking history, we did not measure pulmonary function before and after the procedure. Inoue et al[9] investigated the effect of intramuscular atropine and inhaled ipratropium bromide on pulmonary function under topical anesthesia in 29 patients; they concluded that topical lidocaine anesthesia caused bronchoscopy to have a deleterious effect on pulmonary function, inhaled ipratropium bromide protects against these deleterious effects, whereas intramuscular atropine does not. Another study [9] found that both atropine and glycopyrrolate improved pulmonary mechanics before general anesthesia, and neither of them had protective effects on the deterioration after the procedure in 44 patients under general anesthesia. For the small number of the two studies, we need to be cautious of the results. In addition, it is difficult to state the cause of deterioration due to the anticholinergic premedication or amnestic during bronchoscopy.

Our present study also has limitations. We only included patients under general anesthesia and cannot comment on whether the results under topical anesthesia would be the same. The bronchoscopy was performed by multiple, different operators which may introduce some bias or effects in procedure time. We did not compare the atropine and ipratropium bromide. Our initial study design did include an atropine group; however we removed it because we used nebulized ipratropium bromide and atropine cannot be nebulized. A direct comparison would be difficult with different administration methods. The small number of patients in the study limits the statistical power; further studies with larger sample sizes are needed.

Although nebulizing ipratropium bromide achieved its benefit for patients, the safety should be concerned. Our data showed that nebulizing ipratropium bromide significantly increased the hypertension, which indicated that clinicians should be careful to apply this to patients with high risk of hypertension. A cohort study also found an increased risk of cardiovascular events associated with the use of ipratropium bromide in patients with chronic obstructive pulmonary disease.[21]

5. Conclusion

Our results suggest that nebulized ipratropium bromide prior to bronchoscopy is a more effective regimen that shows practical benefit to airway secretion and patient comfort. However, Hypertension was significantly increased, whereas other complications, especially trachycardia, were not. Our data support that routine nebulized ipratropium bromide premedication for bronchoscopy could be useful and beneficial with cautious of complications.

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