

Effects of Tiotropium Combined with Theophylline on Stable COPD Patients of Group B, D and its Impact on Small Airway Function: A Randomized Controlled Trial

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ABSTRACT

Introduction: Tiotropium bromide has been widely used in clinical practice, while theophylline is another treatment option for chronic obstructive pulmonary disease (COPD). However, only a few relevant studies have investigated the long-term outcomes and efficacy of both in patients with COPD. We evaluated the effects of tiotropium and low-dose theophylline on stable COPD patients of groups B and D.

Methods: Eligible participants ($n = 170$) were randomized and received either tiotropium 18 μg once daily with theophylline 100 mg twice daily (Group I) or tiotropium 18 μg once daily (Group II) for 6 months. COPD assessment

test (CAT), modified Medical Research Council (mMRC) dyspnea scores and pulmonary function tests were measured before randomization and during the treatment.

Results: After 6 months of treatment, the CAT scores in both groups decreased significantly (11.41 ± 3.56 and 11.08 ± 3.05 , $p < 0.0001$). The changes of CAT ($p = 0.028$) and mMRC scores ($p = 0.049$) between the two groups differed after 1 month of treatment. In Group I, forced expiratory flow after 25% of the FVC% predicted (MEF_{25%} pred) was significantly improved after 3 months ($4.84 \pm 8.73\%$, $p < 0.0001$) and 6 months ($6.21 \pm 8.65\%$, $p < 0.0001$). There was a significant difference in small airway function tests (MEF_{50%} pred, MEF_{25%} pred, and MMEF% pred) between the two groups after 6 month of treatment ($p = 0.003$, $p < 0.0001$, and $p = 0.021$, respectively).

Conclusions: Tiotropium combined with low-dose theophylline significantly improved the symptoms and general health of patients with stable COPD of groups B and D after 6 months of follow-up. Additionally, this therapy also improved the indicators of small airway function.

Trial Registration: Chinese Clinical Trial Registry (Registry ID: ChiCTR1800019027).

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation [1], and its morbidity and mortality rates are on the rise. Globally, the COPD burden is projected to increase in the future owing to the continued exposure to COPD risk factors and population aging [2]. Other important factors contributing to the burden are patients' lack of knowledge of COPD, their denial of pulmonary function testing and reasonable standard treatments, and poor patient compliance to prescribed medications in the stable period. Therefore, the treatment of COPD, especially the management of stable COPD, is particularly important.

In 2011, the global initiative for chronic obstructive lung disease (GOLD) guidelines proposed that stable COPD patients should be divided into four groups (A, B, C, and D) according to the clinical symptoms and risk of future acute exacerbation [3]. The symptom scores of patients in groups B and D were higher than those in groups A and C, which indicates that the former COPD group patients have more prominent respiratory symptoms, such as chronic cough, sputum production and dyspnea. Moreover, several studies have suggested that the proportion of COPD patients in groups B and D are higher than in groups A and C [4–7]. The GOLD 2017 guidelines recommend long-acting anticholinergic agents (LAMAs) as the preferred treatment in different groups of stable COPD [1]. Previous studies have shown that inhaled tiotropium relieves symptoms and improves the pulmonary function and quality of life [8–10]. There have been numerous reports on the use of tiotropium in COPD patients in China, but few are randomized controlled clinical trials with a large sample size.

Oral slow-release theophylline is widely used as a bronchodilator. Kanehara et al. found low-dose theophylline not only improved forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and forced expiratory volume in 1 s% predicted (FEV₁% pred), but also improved the small airway function [11]. However, Berger and Smith, showed that theophylline could not improve the

small airway function [12]. Because of the differences noted by the aforementioned studies, the effects of low-dose theophylline on the small airway function in patients with stable COPD remain controversial. In addition, limited research has been performed using the combination of tiotropium bromide and theophylline in China and abroad. Thus, the efficacy of this combination needs to be further clinically evaluated.

Therefore, we conducted a prospective randomized controlled trial to investigate the effects of tiotropium alone and tiotropium combined with low-dose theophylline in patients with stable COPD of groups B and D.

METHODS

The study was performed at the West China Hospital of Sichuan University. The protocol was designed in accordance with good clinical practice and the latest revisions to the Declaration of Helsinki. The study was approved by the institutional ethics committees of the West China Hospital of Sichuan University, and it has been registered at <http://www.chictr.org.cn/ChiCTR1800019027>. All participants gave informed consent, and all work was conducted in accordance with the Declaration of Helsinki (1964).

Patients

Outpatients with a clinical diagnosis of stable COPD were recruited from March 2015 to June 2016 in the West China Hospital of Sichuan University, China. The inclusion criteria were as follows: confirmed COPD of groups B and D by pulmonary physicians based on the 2015 GOLD guidelines [13], age ≥ 40 years, and absence of exacerbations [13] for at least 1 month. Exclusion criteria: patients used LAMAs, long-acting β_2 -adrenergic agonists (LABAs), inhaled glucocorticoids, oral or intravenous glucocorticoid in the previous 1 month, with any infection in the previous 1 month before study entry, with proved prostatic hyperplasia, bladder neck stenosis or narrow angle glaucoma, or with other clinically significant lung diseases (e.g., asthma, bronchiectasis,

cancer or tuberculosis). We used group design mean comparison to estimate sample size, and the calculation formula was $n = 2 (Z_{\alpha} + Z_{\beta})^2 \sigma^2 / \delta^2$, $Z_{\alpha/2} = 1.96$, $Z_{\beta} = 0.842$, $\sigma = 3.08$, $\delta = \pi_2 - \pi_1 = 1.45$; each group needed 56 cases, a total of 142 cases in the two groups, plus 20% of the withdrawal cases (about $142 \times 0.2 = 28$ cases), and the total estimated sample size was 170 patients.

Study Design

We conducted a 6-month, randomized, controlled, parallel-group open-label trial. Eligible participants were then randomly assigned (1:1) using a computer-generated randomization list to one of two arms: Group I: tiotropium 18 μg once daily by Handihaler (Boehringer Ingelheim Pharma, Ingelheim, Germany) plus slow-release theophylline 100 mg twice daily by oral (Maite Xing Hua Pharmaceutical Factory, Guangzhou, China) group; Group II: tiotropium 18 μg once-daily group. None of the patients was treated with oral prednisolone, LABAs, antihistamines, antileukotrienes, or cromolyn throughout the study.

The treatment duration was 6 months, with clinical visits at the end of the first month (visit 2), the third month (visit 3) and the sixth month (visit 4). During the treatment, subjects with any of the following conditions were removed from the study: combined with acute exacerbations; poor compliance (taking $< 80\%$ or $> 120\%$ of the dosage); occurring serious adverse events; combined with any one of the above exclusion criteria.

Pulmonary Function Test

The spirometry was performed before and after inhalation of a bronchodilator. We recorded the following indicators: FVC, FEV₁, FEV₁% pred, FEV₁/FVC, peak expiratory flow% predicted (PEF% pred), forced expiratory flow after 75% of the FVC% predicted (MEF₇₅% pred), MEF₅₀% pred, MEF₂₅% pred, maximal mid-expiratory flow% predicted (MMEF% pred). PEF% pred and MEF₇₅% pred are the indicators of airflow in large airways; MEF₅₀% pred, MEF₂₅% pred, and MMEF% pred are the indicators of airflow in small airways.

Outcome Measurements

The primary outcomes included COPD assessment test (CAT) score, the modified British Medical Research Council (mMRC) dyspnea scale score and pulmonary function test indicators at baseline and each visit. According to COPD-related minimal clinically important differences, lung function of FEV₁ should increase 100 ml, while modified Medical Research Council (mMRC) dyspnea scores should decrease 1 unit [14]. The secondary outcomes were acute exacerbations and adverse events.

Statistical Analysis

All statistical analysis was performed using SPSS 20.0 (IBM, Chicago, IL, USA), and a p value < 0.05 was considered statistically significant. Means and standard derivations (SD) are used for those variables with normal distributions. Other variables are expressed as medians and inter-quartile ranges. Dichotomous variables (COPD exacerbations, complications, adverse events) were reported as frequencies and proportions.

The demographic data, clinical data, and outcome indexes were compared between the two groups at baseline and each visit. For variables with normal distribution, we used the independent sample t test, while for non-normal data, we used the independent samples Mann–Whitney U test. When comparing the symptom scores and lung function of the two arms between baseline and each visit, we used the paired sample t test if the data had normal distribution, otherwise we used the Wilcoxon signed-rank test. The Chi squared test was used to compare the rates of complications and adverse events of the two groups.

RESULTS

Subjects

Patients were enrolled between March 2015 and June 2016. A total of 170 subjects underwent randomization, 164 subjects (96.5%) completed

the first visit after 1 month of treatment, 155 subjects (91.2%) completed the second visit after 3 months of treatment, finally, 142 subjects (83.5%) completed the third visit after 6 months of treatment. The enrollment and outcomes are shown in Fig. 1. Baseline characteristics of the two groups were similar (Table 1).

CAT and mMRC Score

CAT and mMRC scores of two groups decreased significantly after treatment (Tables 2, 3). After 1 month of treatment, the mean decreases of CAT and mMRC scores in Group I was more prominent than in Group II ($p = 0.028$ and $p = 0.049$, respectively), while, this effect was not observed after 3 months and 6 months of treatment (Fig. 2; Table 4).

Pulmonary Function

In Group I, the median baseline FVC level was 2.38 L, the median FVC levels of subjects who completed the second, third and fourth visit were 2.51 L, 2.54 L (compared with baseline, $p < 0.05$) and 2.63 L (compared with baseline, $p < 0.001$), respectively; the median baseline FEV₁ level was 1.19 L. The median FEV₁ levels of subjects who completed the second, third and fourth visit were 1.28 L, 1.32 L (compared with baseline, $p < 0.05$) and 1.36 L (compared with baseline, $p < 0.05$), respectively (Table 2). In Group II, the median baseline FVC level was 2.31 L. The median FVC levels of subjects who completed the second, third and fourth visit were 2.36 L, 2.44 L (compared with baseline, $p < 0.05$) and 2.48 L (compared with baseline, $p < 0.05$), respectively; the median baseline FEV₁ level was 1.19 L, the median FEV₁ levels of subjects who completed the second, third and fourth visit were 1.24 L, 1.29 L (compared with baseline, $p < 0.001$) and 1.31 L (compared with baseline, $p < 0.05$), respectively (Table 3). Similarly, the other pulmonary function indicators (FEV₁% pred, FEV₁/FVC, PEF% pred, MEF₇₅% pred, MEF₅₀% pred) increased significantly in both groups (compared with baseline, $p < 0.05$) after 3 months and 6 months of treatment (Tables 2, 3).

The small airway function (MEF₂₅% pred and MMEF% pred) increased in Group I (compared with baseline, $p < 0.05$) after 3-month and 6-month treatment, while, this effect was not observed in Group II (Tables 2, 3). After 1 month of treatment, MEF₅₀%, MEF₂₅% pred and MMEF% pred level in Group I changed by a mean (SD) of $3.28 \pm 8.70\%$, $3.81 \pm 9.71\%$ and $1.84 \pm 8.50\%$, respectively, none of which with statistical difference compared with Group II. After 3-month treatment, MEF₅₀%, MEF₂₅% pred and MMEF% pred level in Group I changed by a mean (SD) of $4.38 \pm 8.57\%$, $4.84 \pm 8.73\%$ and $2.70 \pm 8.65\%$, respectively, MEF₂₅% pred showed statistical difference compared with Group II ($p = 0.004$). After 6 months of treatment, MEF₅₀%, MEF₂₅% pred and MMEF% pred level in Group I changed by a mean (SD) of $5.77 \pm 8.79\%$, $6.21 \pm 8.65\%$ and $3.64 \pm 9.20\%$, respectively, all of which had statistical difference compared with Group II (Fig. 2).

Adverse Events

Adverse events in each group are summarized in Table 5. Four and five serious adverse events were observed in the combination therapy group and the tiotropium-alone group, respectively. In addition to the one patient who was hospitalized for spinal surgery in the combination therapy group and one patient who was hospitalized due to acute appendicitis in the tiotropium-alone group, the rest of hospitalizations were due to acute exacerbations of COPD. No recruited subjects had vicious events associated with adverse events, and no deaths occurred.

DISCUSSION

Our study was a prospective randomized controlled trial. We innovatively selected patients with groups B and D COPD with severe symptoms as research participants. We used LAMA, which is recommended by GOLD 2017 for each group of stable COPD patients, as the control therapy. This is the first study to explore the effect of low-dose theophylline combined with tiotropium bromide on small airway function in

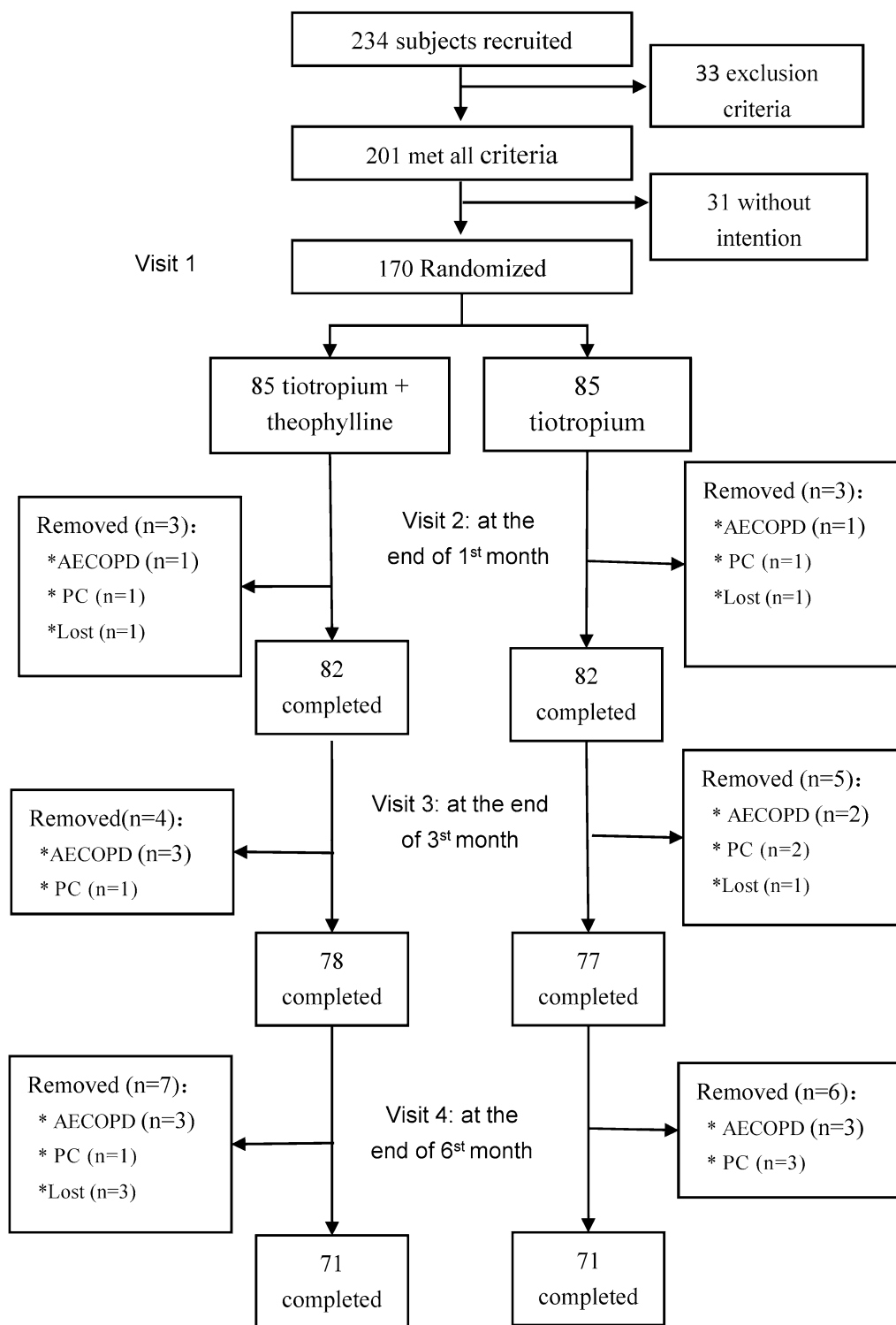


Fig. 1 Enrollment and outcomes. *AECOPD* acute exacerbation of chronic obstructive pulmonary disease, *PC* poor compliance

Table 1 Demographic and clinical characteristics of patients with COPD at baseline

	Group I	Group II	<i>p</i> value
<i>n</i>	85	85	
Age, years	62.27 ± 8.03	64.52 ± 8.22	0.140
Male, <i>n</i> (%)	70 (82.3)	68 (80.0)	0.854
BMI, kg/m ²	22 ± 3.01	22.4 ± 3.86	0.439
Smoking status, <i>n</i> (%)			0.710
Never	17 (20.0)	20 (23.5)	
Current	27 (31.8)	21 (24.7)	
Previous	41 (48.2)	44 (51.8)	
Pack-years smoked ^a	40.5 (11.5–45)	35 (15–50)	0.193
GOLD stage, <i>n</i> (%)			0.914
GOLD 1	3 (4)	4 (5)	
GOLD 2	25 (29)	33 (39)	
GOLD 3	47 (55)	25 (29)	
GOLD 4	10 (12)	23 (27)	
Cor pulmonale, <i>n</i> (%)	18 (21)	19 (22)	0.853
Home oxygen therapy, <i>n</i> (%)	6 (7)	5 (6)	0.883
Exacerbation history ^a	2 (1–2)	1 (1–2)	0.552
CAT score	20.89 ± 4.25	22.19 ± 4.47	0.055
mMRC dyspnoea score, <i>n</i> (%)			0.409
0	0	0	
1	1 (1.2)	0 (0)	
2	35 (41.2)	32 (37.6)	
3	47 (55.3)	49 (57.6)	
4	2 (2.3)	4 (4.8)	
FVC (L)	2.38 ± 0.82	2.31 ± 0.76	0.547
FEV ₁ (L)	1.19 ± 0.52	1.19 ± 0.5	0.315
FEV ₁ % pred	46.55 ± 15.94	46.56 ± 18.98	0.999
FEV ₁ /FVC (%)	49.98 ± 9.59	48.61 ± 12.2	0.415
PEF% pred	40.47 ± 18.85	39.24 ± 19.16	0.672
MEF ₇₅ % pred	21.9 ± 12.46	23.02 ± 16.35	0.615
MEF ₅₀ % pred	17.35 ± 10.25	17.58 ± 12.84	0.898
MEF ₂₅ % pred	19.1 ± 11.58	20.04 ± 11.87	0.599
MMEF% pred	17.11 ± 9.13	18.16 ± 12.36	0.528

Table 1 continued

	Group I	Group II	<i>p</i> value
Complications, <i>n</i> (%)			
Cardiovascular disease	11 (12.9)	12 (14.1)	0.832
Hypertension	10 (11.8)	14 (16.5)	0.509
Diabetes	3 (3.5)	1 (1.2)	0.621

Group I: tiotropium 18 µg once-daily + theophylline 100 mg twice-daily groups, Group II: tiotropium 18 µg once-daily group

Data presented as mean (SD) unless specified

BMI body mass index, *GOLD* global Initiative for Chronic Obstructive Lung Disease, *CAT* COPD assessment test, *mMRC* modified Medical Research Council, *FVC* forced vital capacity, *FEV₁* forced expiratory volume in one second, *FEV₁% pred* forced expiratory volume in one second% predicted, *PEF% pred* peak expiratory flow% predicted, *MEF_{75%} pred* forced expiratory flow after 75% of the FVC% predicted, *MEF_{50%} pred* forced expiratory flow after 50% of the FVC% predicted, *MEF_{25%} pred* forced expiratory flow after 25% of the FVC% predicted, *MMEF% pred* maximal mid expiratory flow% predicted

^a Mean (range). Pack-years smoked, packs of cigarette per day × smoking years

patients with COPD. We demonstrated that add-on therapy with low-dose theophylline significantly improved the symptom scores and pulmonary function, especially small airway function in patients with stable COPD of groups B and D who are already on tiotropium treatment.

Previous studies have shown that inhaled tiotropium relieves symptoms and improves the pulmonary function and quality of life in COPD patients [8, 15, 16]. The 1-year Prevention Of Exacerbations with Tiotropium in COPD (POET-COPD) trial [17] showed that tiotropium was more effective than salmeterol in preventing exacerbations in 7376 patients with moderate-to-very-severe COPD. A meta-analysis comparing the relative clinical effects of tiotropium and LABAs revealed that, although both were similar in symptom improvement and changes in lung function, tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations [18]. Recently, Suissa et al. showed that COPD treatment initiation with tiotropium compared with LABAs does not increase cardiovascular risk in the first year of treatment [19]. The above studies tend to show that tiotropium is superior to LABAs; therefore, we chose tiotropium as the control therapy.

The 1-month short-term follow-up results showed that the CAT scores and mMRC dyspnea scores decreased significantly in both groups, suggesting that both combination therapy and tiotropium alone could improve the symptoms of COPD patients. We also found that the changes of CAT and mMRC scores between the two groups after treatment were significant. It is suggested that the combined treatment could alleviate the symptoms of COPD patients in a short time, which is consistent with the results of several studies. A randomized controlled study conducted by Kawayama et al. compared effects of tiotropium combined with theophylline versus theophylline alone on lung function (including FVC, FEV₁, and PEF) and mMRC scores in stable COPD patients; the combination treatment was superior to the latter in all respects [20].

A previous study showed that therapy with tiotropium improved the absolute value of FVC and FEV₁ during a 4-year follow-up period in patients with COPD [8]. Our results indicated that the combination of low-dose theophylline and tiotropium could not improve the lung function in stable COPD patients in the short term, but improved the absolute values of FVC and FEV₁ in the long term. Kohansal et al.

Table 2 Changes in symptom scores and lung function of subjects in Group I during 6 months of therapy

	Visit 1	Visit 2	Visit 3	Visit 4
<i>n</i>	85	82	78	71
CAT score	20.89 ± 4.25	15.38 ± 3.01**	12.34 ± 2.87**	9.39 ± 2.43**
mMRC score ^a		**	**	**
FVC (L)	2.38 ± 0.82	2.51 ± 0.79	2.54 ± 0.79*	2.63 ± 0.91**
FEV ₁ (L)	1.19 ± 0.52	1.28 ± 0.57	1.32 ± 0.59*	1.36 ± 0.59*
FEV ₁ % pred	46.55 ± 15.94	48.67 ± 17.91	50.90 ± 18.03*	51.92 ± 18.40**
FEV ₁ /FVC (%)	49.98 ± 9.59	50.87 ± 11.09	51.45 ± 10.77**	52.12 ± 11.14*
PEF% pred	40.47 ± 18.85	46.67 ± 19.75**	46.76 ± 18.66**	47.07 ± 19.54**
MEF ₇₅ % pred	21.9 ± 12.46	25.85 ± 18.36*	27.12 ± 17.89**	28.52 ± 18.46**
MEF ₅₀ % pred	17.35 ± 10.25	20.90 ± 13.76*	21.89 ± 14.23**	23.32 ± 14.40**
MEF ₂₅ % pred	19.1 ± 11.58	23.12 ± 15.13*	24.25 ± 14.33**	25.50 ± 14.27**
MMEF% pred	17.11 ± 9.13	19.1 ± 11.49	19.93 ± 11.99*	20.86 ± 12.50**

Group I: tiotropium 18 µg once-daily + theophylline 100 mg twice-daily group; Visit 1: at the beginning of therapy; Visit 2: at the end of 1 month- of herapy; Visit 3: at the end of 3 months of therapy; Visit 4: at the end of 6 months of therapy
Data presented as mean (SD) unless specified

CAT COPD assessment test, FVC forced vital capacity, FEV₁ forced expiratory volume in one second, FEV₁% pred forced expiratory volume in one second% predicted, PEF% pred peak expiratory flow% predicted, MEF₇₅% pred forced expiratory flow after 75% of the FVC% predicted, MEF₅₀% pred forced expiratory flow after 50% of the FVC% predicted, MEF₂₅% pred forced expiratory flow after 25% of the FVC% predicted, MMEF% pred maximal mid expiratory flow% predicted

^a mMRC index belongs to grade data, and was analyzed by Wilcoxon signed-rank test

*Compared to baseline, $p < 0.05$

**Compared to baseline, $p < 0.001$

found that high airway mucus secretion is related to the FEV₁ decline [21]. Therefore, we have a reason to believe that tiotropium improves FEV₁ by antagonizing the cholinergic receptor and reducing airway mucus secretion. Compared with tiotropium monotherapy, adding theophylline (200 mg twice daily) did not improve FVC and FEV₁ in patients with stable COPD. This was different from Cazzola and Matera's findings, which may be related to several factors [23]. First, their study added formoterol on tiotropium. Second, the follow-up period of 8 weeks was short, while our follow-up was for 6 months. Third, the sample size was small (36 cases). Therefore, further clinical research is required to investigate whether adding oral low-dose theophylline on tiotropium can improve lung function.

Pathological changes characteristic of COPD is found in the airways, lung parenchyma, and pulmonary vasculature [22]. Small airway dysfunction in COPD patients is significant. Our study showed that oral low-dose theophylline added on tiotropium could not significantly improve the small airway function in COPD patients in the short term, but it could alleviate the patient's small airway flow limitation in the long term. Our results were consistent with an 8-week randomized controlled study that showed low-dose theophylline significantly improved lung function in patients with stable COPD [11]. Theophylline can dilate both the central airways and peripheral small airways. A previous study has shown that oral theophylline can reduce gas trapping in COPD patients, which suggests its impact on the

Table 3 Changes in symptom scores and lung function of subjects in Group II during 6 months of therapy

	Visit 1	Visit 2	Visit 3	Visit 4
<i>n</i>	85	82	78	71
CAT score	22.19 ± 4.47	17.51 ± 3.74**	13.97 ± 3.72**	10.37 ± 3.10**
mMRC score ^a	**	**	**	**
FVC (L)	2.31 ± 0.76	2.36 ± 0.55	2.44 ± 0.56*	2.48 ± 0.55*
FEV ₁ (L)	1.19 ± 0.5	1.24 ± 0.49	1.29 ± 0.47**	1.31 ± 0.47*
FEV _{1%} pred	46.56 ± 18.98	50.27 ± 19.51**	51.47 ± 19.92**	53.30 ± 19.43*
FEV ₁ /FVC (%)	48.61 ± 12.2	50.71 ± 12.86*	51.03 ± 12.15*	52.01 ± 11.81*
PEF% pred	39.24 ± 19.16	43.74 ± 18.90**	44.86 ± 19.19**	46.51 ± 19.14*
MEF _{75%} pred	23.02 ± 16.35	26.23 ± 17.73*	26.61 ± 18.06*	27.17 ± 17.45
MEF _{50%} pred	17.58 ± 12.84	19.76 ± 13.82*	19.94 ± 12.95*	20.56 ± 12.42*
MEF _{25%} pred	20.04 ± 11.87	22.09 ± 13.17	21.80 ± 10.85	22.65 ± 11.51
MMEF% pred	18.16 ± 12.36	19.57 ± 12.93	19.72 ± 12.66	20.04 ± 12.50

Group I: tiotropium 18 µg once-daily + theophylline 100 mg twice-daily groups; Visit 1: at the beginning of therapy; Visit 2: at the end of 1 month of therapy; Visit 3: at the end of 3 months of therapy; Visit 4: at the end of 6 months of therapy. CAT COPD assessment test, FVC forced vital capacity, FEV₁ forced expiratory volume in one second, FEV_{1%} pred forced expiratory volume in one second% predicted, PEF% pred peak expiratory flow% predicted, MEF_{75%} pred forced expiratory flow after 75% of the FVC% predicted, MEF_{50%} pred forced expiratory flow after 50% of the FVC% predicted, MEF_{25%} pred forced expiratory flow after 25% of the FVC% predicted, MMEF% pred maximal mid expiratory flow% predicted. Data presented as mean (SD) unless specified.

^a mMRC index belongs to grade data, and was analyzed by Wilcoxon signed-rank test

*Compared to baseline $p < 0.05$

**Compared to baseline, $p < 0.001$

peripheral airways [23]. Recent studies have shown that low-dose theophylline (150–300 mg/day) has an airway anti-inflammatory effect, it inhibits oxidative stress, and regulates immunity [24–27]. Therefore, the mechanism of low-dose theophylline in improving small airway function may be related to its ability to control airway inflammation and relieve airway smooth muscle spasm; however, the specific mechanism remains to be further researched.

The common adverse effects of tiotropium are dry mouth, COPD exacerbation, and respiratory tract infection [28]. The main adverse reactions to oral theophylline are gastrointestinal discomfort, tachycardia, and nervous system symptoms [11], and patients present with nausea, palpitations, and headaches. Our study showed low-dose theophylline combined with

tiotropium was relatively safe in the treatment of patients with stable COPD of groups B and D.

Our study had several limitations. First, we did not have a placebo control group. This is because the selected subjects were stable COPD of groups B and D with severe symptoms and (or) poor lung function; it was not possible to ethically have a placebo control group. Second, the study was an open-label experiment without blinding due to technical conditions and therefore prone to bias. Third, the relationship between therapies and the reduction in COPD exacerbations was not analyzed due to the limitation of follow-up time. Fourth, some subjects had poor compliance, changed treatment themselves and adjusted the drug doses, which resulted in the observations not being comprehensive.

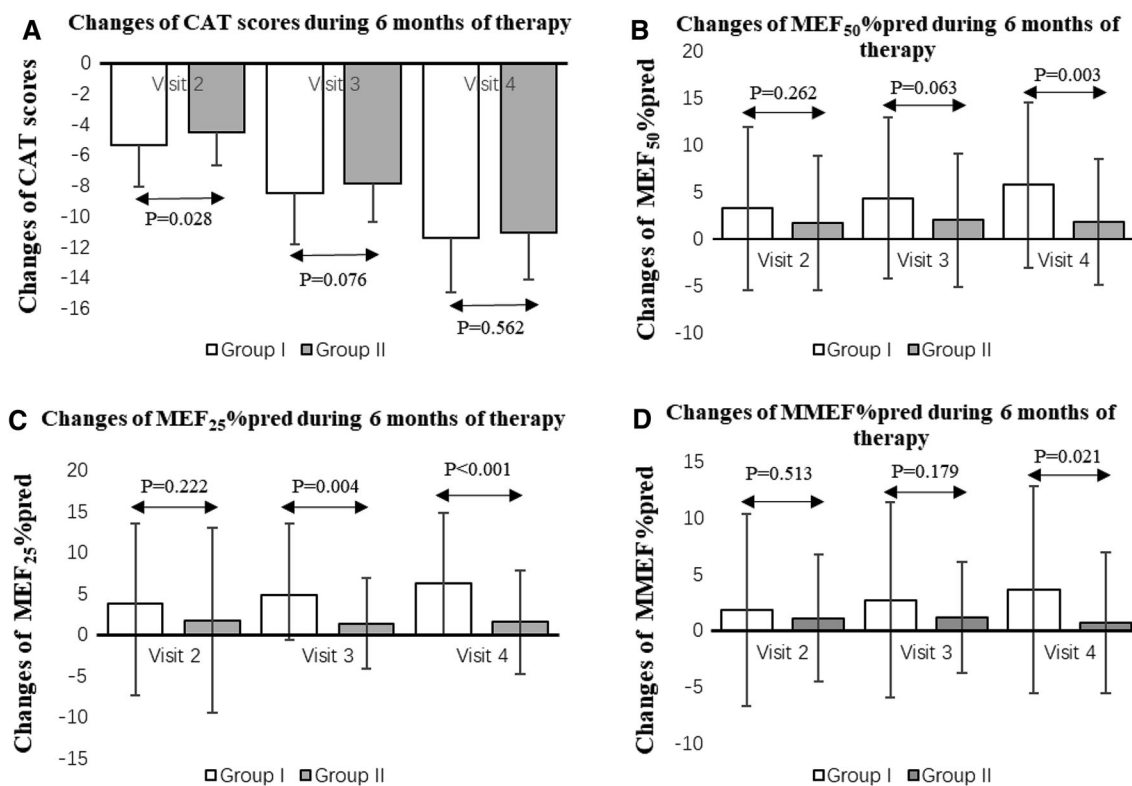


Fig. 2 Treatment differences in terms of **a** CAT, **b** MEF₅₀% pred, **c** MEF₂₅% pred, **d** MMEF% pred during 6 months of therapy. Group I: tiotropium 18 µg once-daily + theophylline 100 mg twice-daily groups, Group II: tiotropium 18 µg once-daily group; Visit 2: at the end of 1 month of therapy; Visit 3: at the end of 3 months of

therapy; Visit 4: at the end of 6 months of therapy. *CAT* COPD assessment test, *MEF₅₀% pred* forced expiratory flow after 50% of the FVC% predicted, *MEF₂₅% pred* forced expiratory flow after 25% of the FVC% predicted, *MMEF% pred* maximal mid expiratory flow% predicted

Table 4 The improvement of mMRC were compared between in two groups during follow-up

Follow-up	Group I		Group II		p value
	Relieved (%)	Not relieved (%)	Relieved (%)	Not relieved (%)	
Visit 2 (n = 164)	42 (51.22)	40 (48.78)	35 (42.68)	47 (57.32)	0.049
Visit 3 (n = 155)	51 (65.38)	27 (34.62)	52 (67.53)	25 (32.47)	0.926
Visit 4 (n = 142)	61 (85.92)	10 (34.62)	57 (80.28)	14 (19.72)	0.926

Group I: tiotropium 18 µg once-daily + theophylline 100 mg twice-daily groups; Group II: tiotropium 18 µg once-daily group; Visit 2: at the end of 1 month of therapy; Visit 3: at the end of 3 months of therapy; Visit 4: at the end of 6 months of therapy

mMRC modified Medical Research Council

CONCLUSION

To conclude, the combination of tiotropium and low-dose theophylline significantly

improved the symptoms and general health of stable COPD patients of groups B and D after 6 months of treatment. In the short period of 1 month, the combination therapy was more

Table 5 Adverse events of two therapy groups

	Group I	Group II	<i>p</i> value
<i>n</i>	85	85	
Total (%)	26 (30.59)	23 (27.06)	0.611
Serious adverse events	4 (4.71)	5 (5.88)	0.732
Death	0	0	
Hospitalization	4 (4.71)	5 (5.88)	0.732
AECOPD hospitalization	3 (3.53)	4 (4.71)	0.700
Non-AECOPD hospitalization	1 (1.18)	1 (1.18)	1.000
AECOPD	7 (8.24)	6 (7.06)	0.773
Dry mouth	13 (15.29)	16 (18.82)	0.541
Dry eyes	3 (3.53)	1 (1.18)	0.312
Palpitation	1 (1.18)	0	0.316
Nausea	1 (1.18)	0	0.316
Rash	1 (1.18)	0	0.316

Group I: tiotropium 18 µg once-daily + theophylline 100 mg twice-daily groups; Group II: tiotropium 18 µg once-daily group

AECOPD acute exacerbation of chronic obstructive pulmonary disease

rapid in significantly relieving symptoms than the monotherapy; therefore, a combination regimen can be considered to relieve symptoms at initial treatment of COPD patients with severe symptoms. Low-dose theophylline (200 mg/day) in combination with tiotropium improved the indicators of small airway function in patients with stable COPD of groups B and D. The specific mechanism of improvement needs further basic research.

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Data Availability. The data sets generated during and/or analyzed during the current

study are available from the corresponding author on reasonable request.

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