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Original Article

Efficacy of tiotropium bromide combined with different doses of fluticasone plus salmeterol DPI in the treatment of stable COPD

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Abstract: Objective: To explore the efficacy of tiotropium bromide combined with different doses of fluticasone plus salmeterol DPI (dry powder for inhalation) in treating stable moderate to severe chronic obstructive pulmonary disease (COPD) and its influence on pulmonary function. Methods: From August 2017 to November 2019, 105 patients with stable moderate to severe COPD in our hospital were enrolled and divided into three groups: group A (GA), group B (GB) and group C (GC). In GA, patients received tiotropium bromide combined with low dose of fluticasone plus salmeterol. In GB, patients received tiotropium bromide combined with medium dose of fluticasone plus salmeterol. In GC, patients received tiotropium bromide combined with high dose of fluticasone plus salmeterol. The baseline data and adverse reactions were observed in each group. After therapy, the improvement of clinical symptoms, quality of life, pulmonary function index and therapeutic effect were observed in each group. Results: There was no difference in the general data of patients among the groups ($P>0.05$). The improvement of clinical symptoms in GB was better than that in GA, and that in GC was better than that in GB ($P<0.05$). There was no difference in adverse reactions among the groups ($P>0.05$). After treatment, IL-8, MPO, LTB4 and the number of inflammatory cells in sputum in the three groups decreased; the four in GB group were dramatically lower than those in GA group, and those in GC group were dramatically lower than those in GB group. The lung function indexes of patients in GB were better than those in GA, and those in GC were better than those in GB ($P<0.05$). The efficacy in GB was better than that in GA, and that in GC was better than that in GB ($P<0.05$). The quality of life scores in GB were higher than those in GA, and those in GC were higher than those in GB ($P<0.05$). Conclusion: Tiotropium bromide combined with high dose of salmeterol xinafoate (SX) and fluticasone propionate (FP) powder for inhalation can effectively improve the pulmonary function of patients with moderate to severe stable COPD.

Keywords: Tiotropium bromide, salmeterol xinafoate and fluticasone propionate, chronic obstructive pulmonary disease

Introduction

COPD is a pervasive systemic disease that can be prevented and treated in clinical practice [1]. Chronic illnesses are the major threat to global health. Approximately two-thirds of deaths in the world are attributed to non-infectious diseases, and the mortality rate of COPD ranks the third in the world [2]. With the aggravation of environmental pollution, the incidence of respiratory diseases is increasing year by year [3]. Although COPD mainly affects the lungs, it is now recognized as a complex and multicomponent disease characterized by chronic systemic inflammation, which is called comorbidity because it often coexists with other diseases [4-7]. Diseases tend to be progressive, and the patients who develop into severe or even extremely severe condition often have great adverse effects on the body, even life-threatening. Therefore, patients with severe COPD should be actively treated to block its development, which has a positive impact on the prognosis of patients. According to the disease manifestations, COPD can be divided into acute attack stage [8] and stable stage [9], and most patients are in stable stage. The main therapeutic objectives for these patients are to reduce the frequency of attacks, avoid complications, ameliorate physical condition, and focus

more on promoting the recovery of lung function and gradually improve the quality of life.

At present, the drugs used to treat COPD mainly include glucocorticoid [10], bronchodilator [11], leukotriene receptor antagonist [12], antioxidant [13] and immunomodulator [14]. Tiotropium bromide is a new anticholinergic drug, which can dilate bronchi for a long time by blocking cholinergic receptors and improve pulmonary ventilation function, so it can be used as a first-line treatment for COPD [15]. SX (salmeterol xinafoate) and FP (fluticasone propionate) powder for inhalation is a compound of salmeterol and fluticasone propionate, and it is a long-acting β_2 receptor agonist, which has the synergistic effect of anti-inflammatory and anti-asthmatic, and can also dilate bronchi by activating β_2 adrenoceptor [16]. This research aimed to compare the efficacy of tiotropium bromide combined with different doses of SX and FP powder for inhalation in treating medium to serious stable COPD and its influence on pulmonary function.

Materials and methods

Research objects

From August 2017 to November 2019, 105 patients with moderate to severe stable COPD treated in Wuhu Traditional Chinese Medicine Hospital were enrolled and retrospectively analyzed (stable period refers to patients with stable or mild symptoms after treatment or natural remission, which can last for more than 2 months), and they were divided into group A, B and C. There were 30 cases in GA, including 19 males and 11 females, with an average age of (68.35±3.11) years. There were 35 cases in GB, including 22 males and 13 females, with an average age of 68.12±3.02 years. There were 40 cases in GC, including 26 males and 14 females, with an average age of 67.91±3.21 years.

Inclusion criteria: Patients met the relevant diagnostic criteria in the Chinese Expert Consensus on Diagnosis and Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) [17]; The standard of moderate to severe degree was 30% FEV_1% pred <80%. Patients had not received anti-infective drugs during the last week before enrollment, and were willing to cooperate with the treatment.

Exclusion criteria: Those who were allergic to the drugs in this study; Patients with respiratory diseases and cardiovascular and cerebrovascular diseases; Patients with liver and kidney dysfunction.

All patients were fully informed of the study and signed the informed consent form. It has been authorized by the hospital ethics committee (WH.2016091596).

Methods

All the patients were treated with tiotropium bromide for inhalation (Zhengda Tianqing Phar= maceutical Group Co., Ltd., SFDA Approval No. H20060454, specification: 18 μg*24 capsules, powder aerosol), 18 μg inhalation, once a day. On this basis, patients in GA, GB and GC were given low, medium and high doses of SX and FP powder (Glaxo Wellcome Production, France, registration number: H20150323, specification, dry powder inhalation), specifically 50 ug/100 μg*60 bubble, 50 ug/250 μg*60 bubble and 50 ug/500 μg*60 bubble, for inhalation, once every time, twice a day.

In all three groups, the patients were treated for three months.

Outcome measures

(1) After treatment, the improvement of clinical symptoms was observed in each group, including four dimensions: expectoration, cough, lung rale and shortness of breath, with 0-3 points for each item and 12 points in total. 0 point: no cough, no shortness of breath, no sputum, no rale; 1 point: intermittent cough, shortness of breath after moving up the third floor, a small amount of sputum (10-15 mL/d), occasional lung rales; 2 points: frequent cough, shortness of breath when walking flat, a moderate amount of sputum (15-50 mL/d), scattered rales in the lungs; 3 points: severe or day and night cough, shortness of breath after slight activity, a severe amount of sputum (>50 ml/d), full of rales in the lungs.

(2) The therapeutic effect was observed in each group. It could be divided into “markedly effective”, “effective” and “ineffective”. Markedly

effective: the clinical manifestations and signs of the patient were improved obviously, the lung rales disappeared or decreased significantly, and the lung function was ameliorated significantly; Effective: the clinical symptoms and signs of the patient were initially improved, the lung rales were reduced, the disease was intermittent, and drugs were still needed to maintain health; Ineffective: The clinical symptoms and signs of the patients did not improve obviously, but worsened, and the lung rales increased. Total effective rate = (markedly effective + effective)/total number × 100%.

(3) The lung function indexes were observed in each group. Before and after treatment, the 6-min walking distance (6 MWD) and lung function indexes were compared among the groups. The lung function was assessed by CAT table of COPD assessment test, including forced expiratory volume in 1 s (FEV_1), FEV_1 as a percentage of the expected value (FEV_1%), and FEV_1/forced vital capacity (FEV_1/FVC).

(4) In each group, the expression levels of serum IL-8 (Human IL-8 ELISA Kit, ab214030, Abcam (Shanghai) Trading Co., Ltd), IL-10 (Human Interferon gamma + IL-10 ELISPOT Set, ab48722, Abcam (Shanghai) Trading Co., Ltd) and TNF-α (Human TNF alpha ELISA Kit, ab181421, Abcam (Shanghai) Trading Co., Ltd) were measured by enzyme-linked immunosorbent assay.

(5) The induced sputum specimens of patients in each group were collected before and after treatment, and the cell survival rate was determined by trypan blue elimination method. The qualified specimens were those with a survival rate >50% and squamous cells <20%. The neutrophils and eosinophils in induced sputum sediment of each group were classified and counted by optical microscope before and after treatment. The sputum supernatant was packaged and frozen at -80°C for subsequent detection.

(6) The frozen sputum supernatant was obtained, and the levels of MPO (Human Myeloperoxidase ELISA Kit (MPO), ab119605, Abcam (Shanghai) Trading Co., Ltd), IL-8 (Human IL-8 ELISA Kit, ab214030, Abcam (Shanghai) Trading Co., Ltd) and LTB4 (Leukotriene B4 ELISA Kit, ab133040, Abcam (Shanghai) Trading Co., Ltd) in the supernatant of induced sputum were detected by double sandwich enzyme-linked immunosorbent assay, and the experiment was conducted in strict accordance with the instructions of the kits.

(7) The adverse reactions were observed in each group. The adverse reactions include tachycardia, slight palpitation, headache, nausea and vomiting, and oropharyngeal dryness.

(8) After treatment, the quality of life (QoL) was observed in each group. The simple scale for physical condition survey (SF-36) [18] was used, which mainly includes the dimensions of physical function, role physical, bodily pain, physical condition, vitality, society function, role emotional, mental health, etc. The full score of each item is 100. The higher the score, the better the quality of life.

Statistical analysis

SPSS20.0 statistical software was used for data processing. GraphPad Prism 8.0 (GraphPad Software, San Diego, USA) was used to plot the images. The quantitative data were represented by mean value ± standard deviation. The comparison between groups was conducted by t test. The comparison among groups was conducted by ANOVA test. The counting data were represented as percentage, and χ^2 test was performed. The difference was statistically significant with $P<0.05$.

Results

Comparison of patient's baseline data

By comparing the baseline data of patients among three groups, we found that there was no statistically significant difference ($P>0.05$), indicating comparability (**Table 1**).

Improvement of clinical symptoms and clinical efficacy of patients in each group

Before treatment, the difference was not statistically significant in scores of clinical symptoms among the three groups ($P>0.05$). After treatment for three months, the clinical symptom scores of patients in GB and GC were obviously higher than those in GA, while those in GC were obviously higher than those in GB. The efficacy in GB was better than that in GA, and that in GC was better than that in GB, with statistically significant difference ($P<0.05$) (**Table 2**).

Table 1. Baseline data of patients

	GA (n=30)	GB (n=35)	GC (n=40)	χ^2/t/F	P
Gender [case (%)]				0.04124	0.9796
Male	19 (63.3)	22 (62.8)	26 (65.0)		
Female	11 (36.7)	13 (37.2)	14 (35.0)		
Age (years)	68.12±3.02	67.91±3.21	68.35±3.11	0.1865	0.8302
Course of disease (years)	8.36±2.15	8.84±2.03	8.51±2.32	0.4228	0.6563
Disease degree [case (%)]				0.1199	0.9418
Moderate	17 (56.7)	19 (54.3)	21 (52.5)		
Severe	13 (43.3)	16 (46.7)	19 (47.5)		
Types of comorbidities [cases (%)]				0.3316	0.9877
Bronchial asthma	13 (43.3)	16 (45.7)	18 (45.0)		
Pulmonary tuberculosis	9 (30.0)	10 (28.6)	10 (25.0)		
Bronchiectasis	8 (26.7)	9 (25.7)	12 (30.0)		

Table 2. Comparison of clinical symptoms and clinical efficacy of patients in each group

	Clinical symptom score			Clinical efficacy [cases (%)]			Total effective rate
				Markedly effective	Effective	Ineffective	
GA (n=30)	Before treatment		7.12±1.05	12 (40.0)	5 (16.7)	12 (43.3)	17 (56.7)
	After treatment for 3 months		5.26±1.15				
GB (n=35)	Before treatment		7.05±1.31	21 (60.0)	7 (20.0)	7 (20.0)	28 (80.0)
	After treatment for 3 months		4.71±0.94				
GC (n=40)	Before treatment		7.10±1.24	28 (70.0)	10 (25.0)	2 (5.0)	38 (95.0)
	After treatment for 3 months		4.09±0.81				
GB vs. GA	χ^2/t	Before treatment	0.2349				4.1291
		After treatment	2.1215				
	P	Before treatment	0.8149				0.0422
		After treatment	0.0378				
GC vs. GB	χ^2/t	Before treatment	0.1696				3.9771
		After treatment	3.0685				
	P	Before treatment	0.8657				0.0461
		After treatment	0.0030				

Pulmonary function of patients in each group

Before treatment, the difference was not statistically significant in 6-min walking distance, FEV_1, FEV_1% and FEV_1/FVC among the three groups (P>0.05). After treatment, the differences of the above indicators among the 3 groups were statistically significant (P<0.05). The lung function indexes of patients in GB were better than those in GA, and those in GC were better than those in GB (**Figure 1**).

Levels of serum inflammatory factors in each group

Before treatment, the levels of various inflammatory factors in serum of the three groups were compared, and there was no statistically significant difference among the three groups (P>0.05). After treatment for 3 months, the levels of IL-10 in the three groups were higher than those before treatment, and the levels of IL-8 and TNF-α in the three groups were lower than those before treatment. The indexes in GB were better than those in GA but inferior to those in GC, with statistically significant differences (P<0.05) (**Figure 2**).

Levels of inflammatory factors in sputum of patients in each group

Before treatment, there was no obvious difference in the levels of sputum IL-8, MPO and LTB4 among the three groups (all P>0.05). After

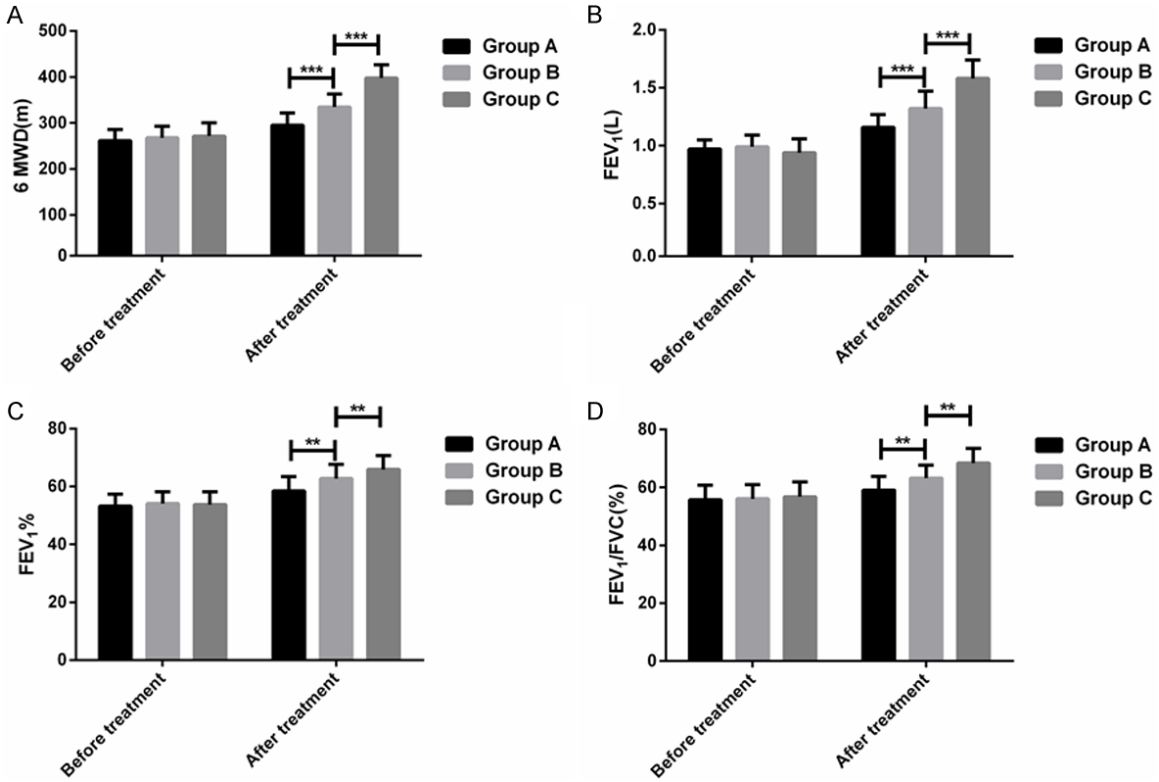

Figure 1. Pulmonary function of patients in each group. A. 6-min walking distance of patients in the three groups; B. Expiratory volume at the end of the first second in the three groups; C. Percentage of expiratory volume at the end of the first second in the three groups to the predicted value; D. FEV_1/forced vital capacity; **P<0.01, ***P<0.001.

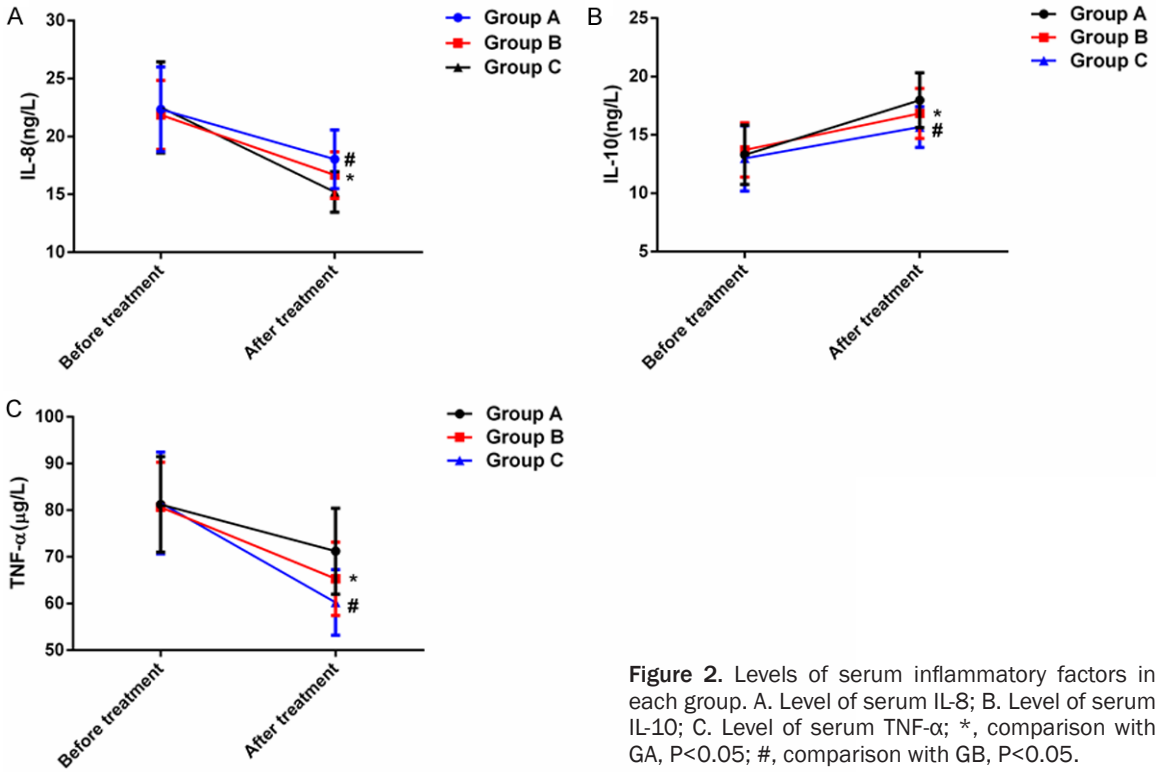

Figure 2. Levels of serum inflammatory factors in each group. A. Level of serum IL-8; B. Level of serum IL-10; C. Level of serum TNF-α; *, comparison with GA, P<0.05; #, comparison with GB, P<0.05.

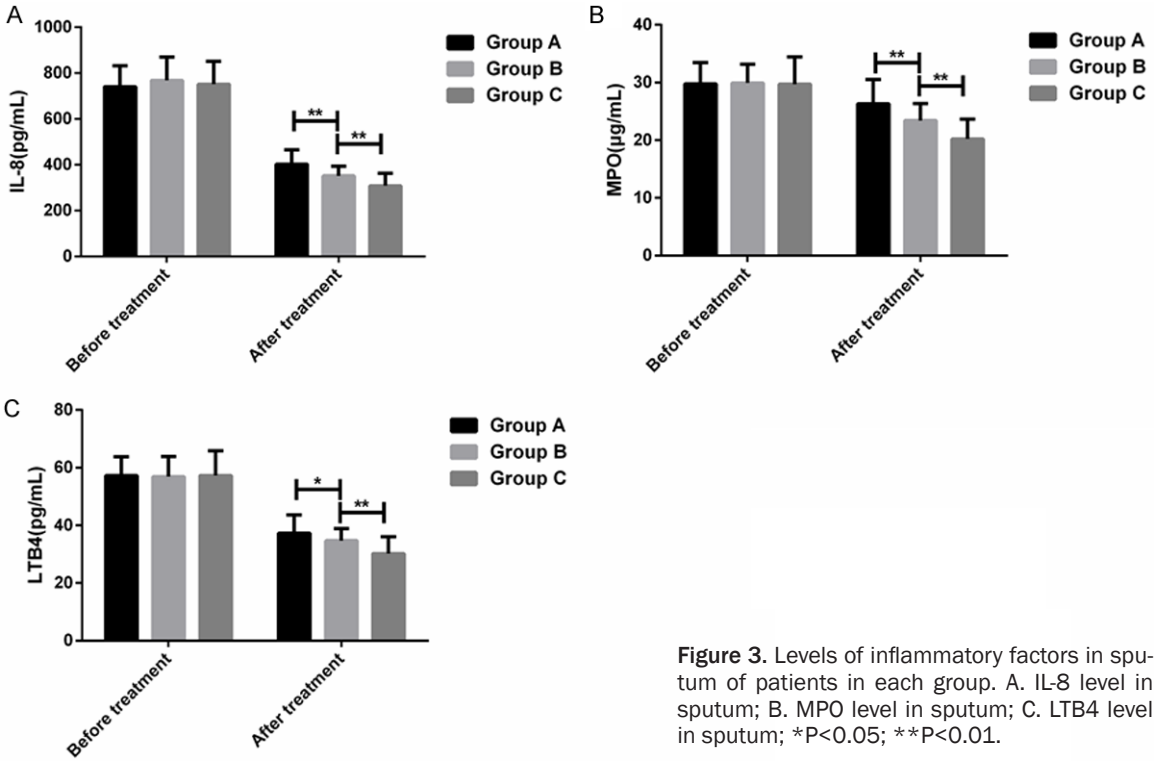

Figure 3. Levels of inflammatory factors in sputum of patients in each group. A. IL-8 level in sputum; B. MPO level in sputum; C. LTB4 level in sputum; *P<0.05; **P<0.01.

treatment, the levels of sputum IL-8, MPO and LTB4 in the three groups all decreased, and significantly lower levels in GB than those in GA and significantly lower levels in GC than those in GB were found (all P<0.05) (**Figure 3**).

Comparison of inflammatory cells in sputum of patients in each group

Before treatment, there was no statistically significant difference in inflammatory cells of induced sputum among the three groups (P>0.05). After treatment, the inflammatory cells of induced sputum in the three groups were lower than those before treatment, the cells in GB were lower than those in GA, and the cells in GC were lower than those in GB. The differences were statistically significant (P<0.05) (**Table 3**).

Adverse reactions of patients in each group

In GA, there were 2 patients with tachycardia, 1 patient with slight palpitation, 1 patient with headache, 2 patients with nausea and vomiting and 2 patients with oropharyngeal dryness. In GB, there were 1 patient with tachycardia, 1 patient with headache, 2 patients with nausea and vomiting and 2 patients with oropharyngeal dryness. In GC, there were 1 patient with headache, 1 patient with nausea and vomiting and 2 patients with oropharyngeal dryness. The incidence of adverse reactions in GA, GB and GC was 26.7%, 17.0% and 10.0%, respectively. The difference was not statistically significant among the three groups (P>0.05) (**Table 4**).

Quality of life scores in each group

The quality of life was scored from the aspects of physical function, health status, bodily pain, vitality, emotional role, mental health, role physical and social function. Before therapy, there was no obvious difference in the scores of various indicators among the three groups. After treatment, the QoL scores of patients in GB were higher than those in GA, and those in GC were higher than those in GB, with statistically significant difference (P<0.05) (**Table 5**).

Discussion

During the COVID-19 epidemic, the Global Initiative for COPD defined that patients with COPD should follow foundational infection control measures, including social distance, handwashing and wearing facial masks. The patients

Table 3. Comparison of inflammatory cells in sputum of patients in each group

		Neutrophils		Eosinophils	
		Before treatment	After treatment	Before treatment	After treatment
GA (n=30)		88.45±5.97	83.23±4.12	10.56±2.32	8.10±2.21
GB (n=35)		89.21±6.34	80.21±3.83	10.89±2.64	7.07±1.83
GC (n=40)		88.87±6.02	77.21±2.97	10.33±2.58	6.29±1.52
GB *vs.* GA	χ^2/t	0.4948	2.1585	0.5310	2.0556
	P	0.6224	0.0347	0.5973	0.0439
GC *vs.* GB	χ^2/t	0.2380	3.8147	0.9277	2.0161
	P	0.8125	0.0002	0.3566	0.0474

Table 4. Comparison of adverse reactions among the three groups

		Tachycardia	Slight palpitation	Headache	Nausea and vomiting	Oropharyngeal dryness	Total incidence rate
GA (n=30)		2 (6.7)	1 (3.3)	1 (3.3)	2 (6.7)	2 (6.7)	8 (26.7)
GB (n=35)		1 (2.8)	0	1 (2.8)	2 (5.7)	2 (5.7)	6 (17.0)
GC (n=40)		0	0	1 (2.5)	1 (2.5)	2 (5.0)	4 (10.0)
GB *vs.* GA	χ^2/t						0.8670
	P						0.3518
GC *vs.* GB	χ^2/t						0.8242
	P						0.3640

Table 5. Quality of life scores in the three groups

		Physical function		Health status		Bodily pain		Vitality	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
GA (n=30)		47.25±4.52	57.16±5.18	45.15±5.12	49.61±5.36	53.15±6.25	64.15±6.81	44.25±5.26	48.61±5.04
GB (n=35)		48.61±4.81	64.81±5.84	45.62±4.91	52.82±5.22	52.84±6.17	70.25±6.95	45.05±5.15	51.51±5.26
GC (n=40)		47.94±4.66	68.64±5.71	45.36±5.08	55.68±5.16	53.34±6.28	73.54±6.72	44.81±5.33	54.82±5.09
GB *vs.* GA	χ^2/t	1.1683	5.5440	0.3772	2.4412	0.2007	3.5605	0.6182	2.2589
	P	0.2471	<0.0001	0.7073	0.0175	0.8415	0.0007	0.5386	0.0274
GC vs. GB	χ^2/t	0.6119	2.8674	0.2246	2.3817	0.3468	2.0817	0.1976	2.7662
	P	0.5425	0.0054	0.8229	0.0198	0.7297	0.0408	0.8439	0.0072
		Emotional role		Mental health		Role physical		Social function	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
GA (n=30)		58.15±4.75	63.25±5.02	59.52±5.71	62.04±4.82	42.25±4.25	53.81±5.48	57.25±5.61	62.87±6.34
GB (n=35)		58.26±4.83	65.81±4.71	59.81±5.83	64.41±4.71	43.51±4.85	59.81±5.81	57.91±5.48	65.97±5.57
GC (n=40)		57.79±5.02	68.19±4.15	59.01±5.57	66.57±4.01	42.97±4.68	62.51±5.91	58.06±5.54	68.73±5.73
GB *vs.* GA	χ^2/t	0.0922	2.1192	0.2018	2.0008	1.1048	4.2603	0.4788	2.0987
	P	0.9268	0.0380	0.8407	0.0497	0.2734	<0.0001	0.6337	0.0398
GC *vs.* GB	χ^2/t	0.4117	2.3266	0.6072	2.1453	0.4901	2.2104	0.1175	2.1083
	P	0.6818	0.0227	0.5456	0.0352	0.6255	0.0302	0.9067	0.0384

should be vaccinated in time, especially with influenza vaccine every year. Despite limited data, inhaled corticosteroids, long-acting bronchodilators, roflumilast or chronic macrolides should continue to be used to ensure the stable treatment of COPD. Systemic steroids and antibiotics should be used according to general indications in acute exacerbation of COPD [19].

This research was mainly designed to explore the therapeutic effect of tiotropium bromide combined with different doses of SX and FP

powder for inhalation in treating medium to serious stable COPD and its influence on pulmonary function. Tiotropium bromide is the second generation anticholinergic drug and a new selective anticholinergic bronchodilator, which can selectively antagonize M_1-M_5 cholinergic receptors on bronchial smooth muscles, and its binding force with cholinergic receptors is 10 times stronger than that of traditional ipratropium bromide, which can relax bronchial smooth muscles quickly and effectively relieve dyspnea symptoms [20, 21]. Moreover, it has a strong and lasting effect on bronchial dilation, and its half-life is extremely long. It can improve the bronchoconstriction symptoms of patients at night and keep the respiratory tract unobstructed for 24 hours, effectively preventing and treating the repeated collapse and opening of respiratory tract as well as the friction between the respiratory tissues [22]. SX and FP powder for inhalation is a compound preparation, in which salmeterol is a long-acting β_2 receptor agonist and fluticasone propionate is a glucocorticoid. Both of them cooperate and promote each other in reducing the release of airway inflammatory mediators and inducing neutrophils to play an anti-inflammatory role, so as to play a stronger drug effect [23, 24]. Studies have revealed that inhaled corticosteroids and long-acting β_2 receptor agonists have made breakthroughs in treating COPD [25, 26]. The results uncovered that the improvement of clinical symptoms and lung function of patients receiving tiotropium bromide combined with high-dose SX and FP powder for inhalation was better than that in low-dose and middling-dose groups ($P<0.05$). The results revealed that tiotropium bromide could effectively suppress the release of inflammatory factors, reduce respiratory secretions, keep the respiratory tract unobstructed and improve the pulmonary function of patients. In addition, tiotropium bromide combined with high dose of SX and FP powder for inhalation could promote the relaxation of respiratory smooth muscles, relax bronchus and reduce respiratory edema, and has strong mucus clearance ability and obvious anti-asthmatic effect. There was no difference in adverse reactions among three groups, the side effects of inhalants were small, and the side effects of combined therapy were smaller than those of increasing the dosage alone. Literature reports have revealed that M_3 receptor blockers can obviously block the neutrophil chemotactic activity induced by neurotransmitter acetylcholine. M_3 receptor blockers can reduce the DNA activity induced by acetylcholine, thereby blocking cell proliferation [27]. The results also showed that tiotropium bromide combined with high dose of SX and FP powder for inhalation could reduce the level of neutrophils and eosinophils in induced sputum and improve the level of inflammatory factors in patients. Neutrophils and eosinophils are common inflammatory cells in patients with COPD [28], which aggregate in the airway and secrete inflammatory factors such as IL-8, MPO and LTB4. IL-8 can selectively aggregate neutrophils and activate them, and MPO can reflect neutrophil levels, while LTB4 can aggravate inflammatory reactions [29-31]. IL-10 is an anti-inflammatory cytokine with immunoregulatory function, which participates in inflammatory reaction and immune reaction, so it is crucial for maintaining the balance of immune system [32]. Tiotropium bromide can continuously improve the pathophysiological effects of COPD. Tiotropium bromide combined with high-dose SX and FP powder for inhalation can obviously improve the dynamic over-inflation and dyspnea, significantly reduce and prevent the acute exacerbation of COPD, effectively enhance the quality of life of patients, and ameliorate the long-term prognosis. The results of this research also revealed that the quality of life of patients receiving tiotropium bromide combined with high-dose SX and FP powder for inhalation was obviously higher than that in other groups, with statistically significant difference ($P<0.05$). However, there are some limitations in this study. Neutrophils, lymphocytes and alveolar macrophages are the main indicators of airway cytological changes in COPD, but this study did not include them for analysis. Secondly, patients were not followed up in this study, so whether the two drugs have long-term effects on patients still needs further observation.

To sum up, in this study, we determined that tiotropium bromide combined with high-dose SX and FP powder inhalation can effectively improve pulmonary function in patients with stable moderate to severe COPD, which can decrease the levels of IL-8, MPO and LTB4, thus having crucial application value.

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Disclosure of conflict of interest

None.

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