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Original Article

Salmeterol combined with fluticasone propionate improved COPD in patients during stable stage

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Abstract: Purpose: To evaluate the clinical effect of inhaled Salmeterol with Fluticasone propionate (50:500 μg) in patients with moderate to severe chronic obstructive pulmonary disease (COPD) during the stable stage of the disease. Methods: Sixty patients with moderate to severe COPD were randomly divided into trial and control groups (N=30 each). In the trial group, patients inhaled Salmeterol with Fluticasone (50:500 μg) propionate twice daily via turbuhaler for 3 months. In the control group, patients used slow- released theophylline, 200 mg, twice daily for 3 months; patients took an expectorant (Ambroxol Hydrochloride, 10 ml, three times daily) if necessary. Clinical symptoms and physical signs were graded using St. George's respiratory disease questionnaire (SGRQ). Changes in lung function were assessed. Results: Indicators of lung function including the values of FEV1, FEV1/FVC, and FEV1/predicted values were significantly higher after treatment in the trial group than in the control group ($P<0.05$). SGRQ values in the trial group decreased significantly after treatment ($P<0.05$). Conclusion: Inhaled Salmeterol 50 μg and Fluticasone propionate 500 μg can significantly improve the lung function and clinical symptoms of patients with stable moderate to severe COPD.

Keywords: Salmeterol, COPD, lung function, St. George's respiratory, disease questionnaire

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of illness, death, and consumption of healthcare resources [1, 2]. COPD is associated with high morbidity and increasing mortality, yet its severity is currently underappreciated. Most Chinese patients have moderate to severe COPD. However, the disease is poorly controlled in some patients with mild symptoms [3]. COPD is characterized by inflammation of the lungs in which airflow limitation is not completely reversible and instead increases progressively. It is critical that treatments for COPD be refined in order to improve both the quality and length of life in patients who suffer with it.

Combinations of inhaled corticosteroids and long-acting β2 agonists are widely used for the long term management of COPD [4-9]. Salmeterol, an inhaled long-acting β2 agonists, may improve lung function and health status in symptomatic COPD, whereas Fluticasone propionate, an inhaled corticosteroid, reduces the frequency of acute stage symptom exacerbation and delays deterioration of healthy tissue. Some studies have indicated that the combination of these treatments works better than either component inhaled alone [4, 10, 11]. Importantly, epidemiological studies have shown that use of inhaled corticosteroids may improve survival in chronic obstructive pulmonary disease, particularly when combined with Salmeterol [12]. Also, a short-term treatment with combined inhaled Fluticasone propionate and Salmeterol resulted in greater control of lung function and symptoms than did combined bronchodilator therapy in patients with COPD [8]. In the current study, we hypothesized that Salmeterol with Fluticasone propionate inhalant (50:500 μg) would ameliorate moderate to severe COPD and slow the decline of lung function when other medications had failed to control the disease.

Table 1. Comparison of changes in lung function before and after treatment

Group		Control	Treatment	*t*	*P*
N		30	30		
FEV1	Before Trt	1.0±0.2	1.1±0.1	0.65	>0.05
	After Trt	1.1±0.2	1.4±0.2	2.14	<0.05
t		0.63	2.16		
P		>0.05	<0.05		
FEV1/Predicted values %	Before Trt	39.6±7.2	38.7±7.1	0.65	>0.05
	After Trt	43.8±7.2	48.2±7.2	2.22	<0.05
t		0.69	2.33		
P		>0.05	<0.05		
FEV1/FVC	Before Trt	45.4±7.0	44.7±7.2	0.65	>0.05
	After Trt	46.0±7.0	54.3±7.6	2.59	<0.05
t		0.61	2.63		
P		>0.05	<0.05		

Materials and methods

The investigation reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the People's Hospital of Xinjiang Uygur Autonomous Region.

Ethics statement

The investigation reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the People's Hospital of Xinjiang Uygur Autonomous Region.

Patient population

Sixty patients with COPD were selected randomly from the outpatient [clinic] of the Department of Respiratory Disease between October 2007 and December 2008, 46 of whom were males and 14 females, aged 48 to 79 years (mean 60±10 yrs); diagnosed duration of disease ranged from 5 to 45 yrs, (average 23±12 yrs). Patients were evaluated by medical history, signs, chest X-ray, pulmonary function tests, and the 2002 guidelines for chronic obstructive pulmonary disease treatment of the Chinese Society of the Respiratory Disease Association [13]. Patients with heart, brain, liver, kidney, chronic metabolic diseases, and other lung diseases were excluded. Inclusion criteria for the stable period of the clinical stage and the severity of COPD were as follows: no acute exacerbation history within the previous four weeks; no use of oral, intravenous or inhaled corticosteroids within the previous four weeks; use of long-acting bronchodilators stopped one week before the test, and use of short-acting bronchodilators stopped 24 h prior to testing. Patients who provided informed consent were randomly divided into experimental and control groups. Each group consisted of 30 patients, 23 male and 7 female). Patients were diagnosed with moderate COPD whose percentage of forced expiratory volume in one second (FEV1) over forced vital capacity (FVC) was <70% and whose percentage of FEV1 over predicted value (PV) was 30~80%. Severe COPD was defined by an FEV1/FVC ratio of <70% and a FEV1/PV ratio of <30%. There was no significant difference in age, duration of disease, or fraction of moderate to severe COPD between the experimental and control groups before treatment (P>0.05).

Experimental design

All patients were required to avoid respiratory infections, maintain suitable nutrition, perform breathing exercises, treat with home oxygen if necessary, and avoid smoke irritation. In the control group, patients received slow-releasing theophylline at a dose of 0.2 g, twice a day; and ambroxol hydrochloric acid 10 mL orally when sputum was viscous, three times a day; with albuterol sulfate aerosol (trade name: Ventolin, GlaxoSmithKline Company) for three months. In the experimental group, patients were given salmeterol with fluticasone propionate powder 50:500 μg (trade name: Seretide, GlaxoSmithKline Company), containing 50 μg salmeterol and 500 μg fluticasone propionate per puff inhaled, at a dosage of 1 inhalation twice a day for three months.

Measurements of lung function and life quality

Lung function: Using a pulmonary function analyzer (Jeager MS-PET, Germany) assigned spe-

Table 2. Respiratory score change of clinical symptoms

Group	Treatment	Control	t	p
N	30	30		
Before trt (point)	4.4±1.3	4.3±1.2	0.67	P>0.05
After trt (point)	3.1±1.0*	4.2±1.4	2.70	P<0.05
t	2.69	0.71		
p	P<0.05	P>0.05		

Note: Compared with the control group, *P<0.05.

cialists performed measurements for all patients before treatment and 3 months after treatment. Indicators used were as follows: FEV1, FEV1/FVC %, and FEV1/predicted value %, obtained by measuring repeatedly until the difference between two [successive] measures was less than 5%. The higher value was selected for the measurement results.

Life quality questionnaire: The St. George Respiratory Questionnaire (SGRQ) was applied to evaluate clinical symptoms and signs. Score 0: no cough, no shortness of breath, and no moist rales. Score 1: mild cough, number of coughs <10 times/d, shortness of breath after work, usually without moist rales. Score 2: moderate cough, number of coughs 10 to 20 times/d, shortness of breath after light work, and fine moist rales with deep breath. Score 3: severe cough >20 times/d, shortness of breath at rest, moist rales heard after calm breath. Adverse reactions were recorded during treatment.

Statistical analysis

SPSS 13.0 statistical software was used for statistical analysis. The measurement data are shown as mean ± standard deviation ($\bar{x}\pm s$). Statistical significance was assessed using the t test, with P<0.05 considered significant.

Results

Changes of lung function before and after treatment

There were significant changes in FEV1, FEV1/predicted value %, and FEV1/FVC in the experimental group before and after treatment (P<0.05). There were no significant differences in indicators other than FEV1/predicted value % before and after treatment in the control group. There were significant differences in FEV1, FEV1/predicted value %, and FEV1/FVC between the experimental group and control group after treatment (**Table 1**).

St. George respiratory questionnaire score change before and after treatment

The score of the experimental group decreased significantly after treatment (P<0.05). There was no significant change of score in the control group after treatment (P>0.05). There was significant difference of score between the experimental group and the control group after treatment (**Table 2**).

Adverse reactions

Neither group had any serious adverse reactions. Three patients (10%) in the experimental group had dry throat and nausea, but the symptoms disappeared after the drug was withdrawn. Three patients (10%) in the control group reported adverse reactions, including nausea (2 cases) and palpitation (1 case). There was no significant difference in the number of adverse reactions (P>0.05) between the two groups. All patients had normal levels of blood glucose, blood calcium, and liver and kidney functions before and after treatment. No patient in either group discontinued treatment due to adverse reactions.

Discussion

COPD is a multifactorial inflammatory disease/, in which inflammatory response is related to the severity of the clinical index. A previous study confirmed that COPD patients with stable disease had persistent inflammation [14]. There is currently no effective drug to reverse the deterioration of lung function in COPD. Studies have shown that inhaled corticosteroid combined with a long-acting β2 receptor agonist can reduce the incidence rate of acute exacerbation effectively and improve lung function and quality of life. In particular, inhaled Salmeterol and Fluticasone propionate 50:500 μg was shown to slow the rate of decline of lung function [15, 16]. The Global Initiative for Chronic Obstructive Pulmonary Disease [17] pointed out that the main drugs used to treat moderate to severe COPD with stable stage are hormones combined with inhaled long-acting β2 receptor agonists. Glucocorticoid has a dose-dependent anti-inflammatory effect when used to treat COPD, and can increase the

expression of β2 adrenergic receptor. Salmeterol can accelerate the nuclear translocation of glucocorticoid receptor, promote gene transcription and expression, and enhance the anti-inflammatory effect of the hormone. Combination therapy has a broader anti-inflammatory effect and correlates positively to clinical efficacy [18, 19]. The complementarity of Fluticasone propionate and Salmeterol may enhance the anti-inflammatory effect of treatment and the reduction of airflow limitation. Fluticasone propionate and Salmeterol are fat-soluble drugs. They easily cross the trachea at the deposition site as well as the cell membrane of alveolar epithelial cells to reach their receptors and carry out their functions after inhalation. There is little risk of systemic adverse reactions due to absorption into the bloodstream.

We proposed that patients in the experimental group receive Salmeterol and Fluticasone propionate 50:500 μg to treat moderate to severe COPD, and patients in the control group use slow-release theophylline. The current study has shown that FEV1, FEV1/predicted value %, and FEV1/FVC in the experimental group were higher after treatment than before treatment ($P<0.05$). Improvement of lung function was significantly greater after treatment in the experimental group than in the control group ($P<0.05$). In the control group, there was a significant difference only in FEV1/predictive value % before and after treatment ($P<0.05$). Other indicators did not change significantly ($P>0.05$). There were significant improvements in cough, sputum, shortness of breath, and moist rales in the experimental group compared to those of the control group ($P<0.05$). Patient symptoms and signs improved significantly after three months of treatment. Neither group had any serious systemic adverse reactions. This research demonstrated that inhaled Salmeterol and Fluticasone propionate improved lung function and clinical symptoms better than traditional theophylline treatment in stable stage patients with moderate to severe COPD. Because Salmeterol and Fluticasone propionate 50/500 μg inhalant is expensive, the sample size was small and the observation time limited. The long-term efficacy and safety of Salmeterol and Fluticasone propionate inhalant 50:500 μg in the treatment of COPD in this region needs to be studied further.

Disclosure of conflict of interest

None.

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