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Original Article

Thymopentin and salmeterol-fluticasone for moderate to severe chronic obstructive pulmonary disease and its effect on IgE expression

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Abstract: Objective: To investigate the effect of the combination of salmeterol-fluticasone and thymopentin in patients with moderate to severe chronic obstructive pulmonary disease (COPD), and analyze the effect of combination therapy on immunoglobulin E (IgE) expression. Methods: In this prospective study, 142 patients with moderate to severe COPD were enrolled and randomly divided into the control group and the experimental group according to a random number table, each group including 71 patients. Control group patients received salmeterol-fluticasone inhalation aerosol on the basis of conventional treatment, while patients in the experimental group were given thymopentin added to the treatments received by the patients in the control group. All patients were treated for 3 consecutive months. The clinical efficacy, airway inflammation, IgE expression, pulmonary function, quality of life and adverse events were compared between the control group and experimental group. Results: After treatment, the overall effective rate of the experimental group was higher than the control group ($P<0.05$), and the incidence of overall adverse events was lower ($P<0.05$). Interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-α) in the bronchoalveolar lavage fluid (BALF) in both groups after treatment were lower than before treatment (both $P<0.05$), with lower TNF-α and IL-8 expression in the experimental group than in the control group ($P<0.05$). The levels of serum IgE in both groups after treatment were also lower than those before treatment ($P<0.05$), with lower IgE level in the experimental group than in the control group ($P<0.001$). Additionally, the forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), the ratio of FEV_1 to FVC, and percentage of FEV_1 as predicted (FEV_1% pred) in both groups after treatment were higher than those before treatment (all $P<0.05$), with the experimental groups results superior to the control group (all $P<0.01$). The scores for all the domains of the St George's respiratory questionnaire (SGRQ) in both groups after treatment were lower than those before treatment ($P<0.05$), with a lower score in the experimental group than in the control group ($P<0.05$). Conclusion: The combination therapy of thymopentin and salmeterol-fluticasone resulted in markedly inhibited airway inflammation, and improved humoral immunity, pulmonary function and safety in patients with moderate to severe COPD.

Keywords: Thymopentin, salmeterol-fluticasone, pulmonary function, chronic obstructive pulmonary disease, immunoglobulin E

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease of the respiratory system frequently seen in patients in the Department of Respiratory Medicine, and it has a high incidence. The primary clinical manifestations of the disease are non-reversible and progressive airflow obstruction. If the disease is not managed in time, patients are prone to develop acute exacerbation, which further affects the lungs and develops into acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Even worse, AECOPD may deteriorate in a short time, eventually leading to death from respiratory failure [1, 2]. Due to a large number of smokers and aggravating environmental pollution, results in 25% of the global COPD patients being in China [3]. Currently, the major principle and purpose in treatment of COPD are

to rapidly relieve the symptoms such as dyspnea, prevent acute aggravation of the disease, maximally improve the pulmonary function and health status of patients, and reduce their rates of disability and mortality [4].

Salmeterol-fluticasone is a compound coposed of salmeterol and fluticasone. Thymopentin is an immunomodulator. Previous literature has shown the addition of salmeterol-fluticasone dry powder inhaler to thymopentin has a positive effect on relieving dyspnea and other symptoms in COPD patients, and is helpful to improve their pulmonary functions [5, 6]. Nevertheless, the effect of the above combination therapy on humoral immunity in patients has not been reported. Therefore, the purpose of the present study was to investigate the efficacy of thymopentin in combination with salmeterol-fluticasone in patients with moderate to severe COPD, and to analyze the effect of the combination therapy on humoral immunity in such patients.

Materials and methods

General data

A prospective investigation was conducted among 142 patients with moderate to severe COPD admitted to the hospital from July 2017 to August 2019. All enrolled patients met the diagnosis criteria for moderate and severe COPD in *The Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease* (the 3rd Edition) formulated by the Japanese Respiratory Society in 2011 [7]. Patients were eligible if they had a rate of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) of less than 70%, the percentage of FEV_1 as predicted (FEV_1 % pred) of 30-80% after inhalation of bronchodilators, and an age of 30-70 years, could follow the doctor's advice, had significant airflow obstruction, had not used glucocorticoids within 2 weeks before enrollment, had no previous mental illness, and provided written informed consent. Patients were excluded from the study if they had acute exacerbation of COPD, poor compliance, other pulmonary disease including bronchiectasis and bronchial asthma; had contraindications to glucocorticoid use; had chronic systemic inflammatory disease, malignant tumor, hematopathy or hemorrhagic disease, or hepatic and renal dysfunction or failure, or were pregnant or lactating or allergic to the study drugs. All patients were assigned to the control group (n=71) or the experimental group (n=71) in terms of a random number table. The general data of the two groups are shown in Section 2.1 of the Results. This study was approved by the Medical Ethics Committee of the hospital.

Methods

Treatment strategies such as relieving cough and phlegm and improving asthma were performed for the treatment of patients with moerate to severe COPD in both the control and observational groups, and when necessary, oxygen inhalation was given in some of the patients. Patients in the control group inhaled salmeterol-fluticasone inhalation aerosol (Laboratoire GlaxoSmithKline, France) at 2 presses/time and twice per day. Patients in the experimental group received thymopentin forinjection (Beijing Shuanglu Pharmaceutical, China) in addition to salmeterol-fluticasone inhalation aerosol. Thymopentin for injection was dissolved by adding sterile water for injection (1 mL) before administration, and then intramuscularly injected once or twice per day. The patients in both groups received 3 consecutive months of treatment.

Outcome measures

The general clinical data of patients at baseline were compared between the control and experimental groups. The clinical efficacy of the regmens was also compared between the two groups after treatment: Markedly effectiveness was defined as the disappearance or significant alleviation of symptoms (cough, dyspnea and lung rales) after 5 days of treatment, effectiveness as alleviation of the above symptoms after 5 days of treatment, ineffectiveness as failure to meet the above standards, and existence or aggravation of the above clinical symptoms after 5 days of treatment. The formula for calculating the overall effective rate was as follows: Overall effective rate = Cases of (Markedly effective + effective)/Total cases * 100%. Changes in airway inflammation of patients were compared before and after treatment. Bronchoalveolar lavage fluid (BALF) was collected from each patient, and centrifuged. Subsequently, the changes in inflammatory markers including TNF-α and IL-8 in BALF were tested with the use of a sandwich enzyme-linked immunosorbent assay (ELISA). The

Table 1. Comparison of general data at baseline between the two groups (n, $\bar{x} \pm s$)

Group	Control group (n=71)	Experimental group (n=71)	t/χ^2	P
Male/female	40/31	37/34	0.255	0.613
Age (year)	44.9±4.7	44.2±5.2	0.841	0.402
BMI (kg/m^2)	22.8±3.1	23.6±2.7	1.64	0.103
History of smoking (year)	11.7±3.5	12.1±2.9	0.742	0.46
FEV_1/FVC (%)	64.59±4.13	65.04±4.22	0.642	0.522
FEV_1% pred	40.59±5.39	41.17±5.84	0.615	0.54
COPD grades				
Moderate	43	46	0.271	0.603
Severe	28	25		

Note: BMI: body mass index; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; FEV_1% pred: percentage of FEV_1 as predicted; COPD: chronic obstructive pulmonary disease.

Table 2. Comparison of clinical efficacy between the two groups (n (%))

Group	Control group (n=71)	Experimental group (n=71)	χ^2	P
Markedly effective	22 (30.98)	41 (57.75)	10.23	0.001
Effective	38 (53.52)	27 (38.05)	3.433	0.064
Ineffective	11 (15.49)	3 (4.23)	5.071	0.024
Overall effective rate	60 (84.51)	68 (95.77)	5.071	0.024

changes in patients of IgE expression were compared before and after treatment. Venous blood (5 mL) was collected from each patient, and centrifuged after coagulation, followed by measurement of IgE expression in serum by ELISA. The ELISA kits were purchased from Shanghai Tongwei Industry (Country of origin, Austria). The changes in pulmonary functions of patients were compared before and after treatment. The FVC and FEV_1 were tested by a spirometer (BTL-08 SPIRO, purchased from Zhangqiu shunze Bioengineering, and imported from the UK). The ratio of FEV_1 to FVC and FEV_1% pred were also calculated. Quality of life of patients was evaluated by the St George's respiratory questionnaire (SGRQ) before and after treatment. There was a total score of 100 points for all the domains in the SGRQ, with lower scores indicating better quality of life. Finally, adverse events were calculated and compared between the two groups.

Statistical analysis

Data were analyzed with the use of SPSS, vesion 25.0. Count data were expressed as case/percentage (n/%), and compared between the groups using a chi-square test. Except the incidence of overall adverse events, the rest count data were compared by an adjusted chi-square test. Measurement data were represented by mean ± standard deviation. Between-group comparisons were conducted by independent t tests, while intra-group comparisons were made by means of paired t tests. P<0.05 was considered to be statistically significant.

Results

Comparison of general data at baseline between the two groups

At baseline, the general data including the ratio of male to female patients, mean body mass index (BMI) mean age, and COPD grades differed insignificantly between the two groups, therefore, the two groups were comparable (P>0.05; **Table 1**).

Comparison of clinical efficacy between the two groups

After treatment, 41 patients were markedly effective, 27 were effective, and 3 were ineffective in the experimental group, with an overall effective rate of 95.77%; while 22 patients were markedly effective, 38 were effective, and 11 were ineffective in the control group and overall effective rate was 84.51%. As compared with the control group, the overall effective rate of the experimental group was higher, and the difference was statistically significant (P<0.05). See **Table 2**.

Comparison of airway inflammation between the two groups before and after treatment

The expression of TNF-α and IL-8 in BALF had no significant differences between the experimental and control groups before treatment (P>0.05). After one month's treatment, the standards of IL-8 and TNF-α in BALF in both groups were reduced over that before treatment (P<0.05 or P<0.001); the levels of IL-8 and TNF-α in BALF were lower in the experimental group than in the control group, and the dif-

Table 3. Comparison of airway inflammation between the two groups before and after treatment ($\bar{x}$ ±s) μg/L

Group	Control group (n=71)	Experimental group (n=71)	t	P
TNF-α				
Before treatment	13.29±2.55	13.07±2.16	0.555	0.58
After one month's treatment	12.48±1.87*	11.91±1.04***	2.245	0.026
IL-8				
Before treatment	10.75±1.97	11.03±1.69	0.909	0.365
After one month's treatment	10.14±1.14*	9.70±1.09***	2.351	0.02

Note: TNF-α: tumor necrosis factor-alpha; IL-8: interleukin-8. Compared with the same group before treatment, *P<0.05, ***P<0.001.

Table 4. Comparison of IgE between the two groups before and after treatment ($\bar{x}$ ±s) U/mL

Group	Control group (n=71)	Experimental group (n=71)	t	P
IgE				
Before treatment	1395.60±116.50	1434.07±136.91	1.803	0.074
After treatment	1331.05±98.57***	1138.09±77.78***	11.847	<0.001

Note: IgE: immunoglobulin E. Compared with the same group before treatment, ***P<0.001.

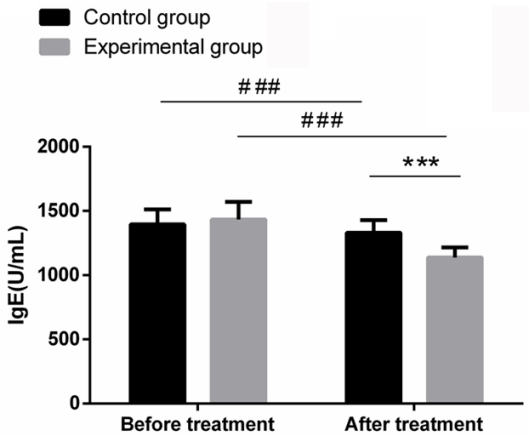

Figure 1. Comparison of IgE between the two groups before and after treatment. IgE: immunoglobulin E. Compared with the before treatment, ###P<0.001; Compared with the control group, ***P<0.001.

ferences were statistically significant (P<0.05). See **Table 3**.

Comparison of IgE between the two groups before and after treatment

The levels of serum immunoglobulin E (IgE) differed insignificantly between the two groups before treatment (P>0.05). However, the levels of serum IgE in both groups after treatment were lower than those before treatment (P< 0.001), with significantly lower serum IgE expression in the experimental group than in the control group (1138.09±77.78 U/mL vs 1331.05±98.57 U/mL; P<0.001; **Table 4** and **Figure 1**).

Comparison of pulmonary function between the two groups before and after treatment

The FEV_1, FVC, the ratio of FEV_1 to FVC, and FEV_1% pred were insignificantly different between the two groups before treatment (P>0.05). Nevertheless, the FEV_1, FVC, the ratio of FEV_1 to FVC and FEV_1% pred in both groups after treatment were higher than those before treatment (P<0.05 or P<0.001); the FEV_1, FVC, the ratio of FEV_1 to FVC, and FEV_1% pred in the experimental group were significantly increased compared to the control group (P<0.01 or P<0.001; **Table 5**).

Comparison of SGRQ scores of the two groups before and after treatment

There were no significant differences in the scores for respiratory symptoms, disease impact and activity ability in the SGRQ between the two groups before treatment (all P>0.05). Compared with before treatment, the scores for all the domains of the SGRQ in both groups were reduce after treatment (P<0.05 or P<0.001); the score for all the domains of the SGRQ in the experimental group was significantly decreased compared with the control group (P<0.05). See **Table 6**.

Adverse events in the two groups

During the treatment, dizziness occurred in 6 patients, drowsiness in 3 patients, and rash, edema and hoarseness in 2 patients each in the control group, with a rate of overall adverse events of 21.13%. In the experimental group, edema occurred in 2 patients, and rash, dizziness and hoarseness occurred in 1 patient

Table 5. Comparison of pulmonary function between the two groups before and after treatment ($\bar{x}$ ±s)

Group	Control group (n=71)	Experimental group (n=71)	t	P
FEV_1 (L)				
Before treatment	1.60±0.44	1.61±0.51	0.125	0.901
After treatment	1.78±0.51*	2.30±0.60***	5.564	<0.001
FVC (L)				
Before treatment	2.33±0.43	2.41±0.51	1.011	0.314
After treatment	2.69±0.40***	2.90±0.48***	2.832	0.005
FEV_1/FVC (%)				
Before treatment	64.59±4.13	65.04±4.22	0.642	0.522
After treatment	75.48±5.10***	90.59±4.30***	19.086	<0.001
FEV_1% pred				
Before treatment	40.59±5.39	41.17±5.84	0.615	0.54
After treatment	43.08±6.30*	49.70±6.60***	6.114	<0.001

Note: FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; FEV_1% pred: percentage of FEV_1 as predicted. Compared with the same group before treatment, *P<0.05, ***P<0.001.

Table 6. Comparison of SGRQ scores of the two groups before and after treatment ($\bar{x}$ ±s)

Group	Control group (n=71)	Experimental group (n=71)	t	P
Respiratory symptoms				
Before treatment	30.09±4.98	30.65±4.33	0.715	0.476
After treatment	28.39±5.20*	26.73±4.50***	2.034	0.044
Disease impacts				
Before treatment	20.04±3.58	19.65±3.90	0.621	0.536
After treatment	18.86±3.20*	17.57±3.46***	2.306	0.023
Activity ability				
Before treatment	31.10±4.39	30.95±5.10	0.188	0.851
After treatment	29.48±4.30*	27.81±3.80***	2.452	0.015

Note: SGRQ: St George's respiratory questionnaire. Compared with the same group before treatment, *P<0.05, ***P<0.001.

Table 7. Adverse events in the two groups (n (%))

Group	Control group (n=71)	Experimental group (n=71)	χ^2	P
Rash	2 (2.82)	1 (1.41)	0	1
Edema	2 (2.82)	2 (2.82)	0.257	0.612
Dizziness	6 (8.45)	1 (1.41)	2.404	0.121
Drowsiness	3 (4.23)	0 (0.00)	1.362	0.243
Hoarseness	2 (2.82)	1 (1.41)	0	1
Overall adverse events	15 (21.13)	5 (7.04)	5.82	0.016

each, with a rate of overall adverse events of 7.04%. The rate of overall adverse events in the experimental group was significantly reduced compared with the control group, and the difference was statistically significant (P<0.05). See **Table 7**.

Discussion

COPD is a clinically common chronic airway inflammatory disease. Its pathogenesis remains to be further explored as it is not fully elucidated. However, one previous study showed that any factors related to pulmonary diseases (such as obstructive emphysema or chronic bronchitis) may induce the presence and development of COPD [8].

Currently, more frequently-used COPD drugs may involve β2-receptor agonists, bronchodilators, inhaled corticosteroids or β2-receptor agonists in combination with inhaled corticosteroids [9-12]. In the present study, salmeterol-fluticasone, a long-acting inhaled compound composed of salmeterol (a β2 receptor agonist) and fluticasone (a corticosteroid), was used for treatment of COPD patients. Salmeterol selectively activates the β2 receptor on airway smooth muscle, thereby dilating the bronchi [13]. In addition, salmeterol acts to reduce vascular permeability and inflammatory exudation, eventually reducing or alleviating the airway swelling in the body of patients. The drug also promotes secretion of bronchial mucus and ciliary movement, and enhances the ventilation function of the lung to a certain extent [14]. Fluticasone, a type of glucocorticoid, binds to glucocorticoid receptor in cells to form a receptor-steroid compound with physiological activity. The compound not only inhibits generation of inflammatory cytokines, but also improves sensitivity of the body to β2 receptor. The addition of the compound to aβ2 receptor agonist also plays a synergistic role in the body of patients [15]. Thymopentin, an immunomodulator extensively used in clinical practice, is primarily utilized to improve cellular immunity in

patients with low immune function, infectious diseases and immune deficiency diseases after radiotherapy and chemotherapy, and it proves to have significant clinical efficacy [16]. In the present study, after treatment, the overall effective rate was up to 95.77%, the incidence of overall adverse events was lower, and the markers for pulmonary function of patients were higher in the experimental group than in the control group; this result suggested that the combination of salmeterol-fluticasone and thymopentin had a positive effect on improving the pulmonary function in patients with moderate and severe COPD. Besides, the combination therapy was superior in safety profile and overall treatment efficacy to salmeterol-fluticasone alone, which is consistent with the finding reported by Bjermer et al. [17].

COPD has shown to be a wide range of diseases characterized by chronic inflammation in the lung parenchyma and the airway. The presence of COPD is associated with chronic inflammation, and is mainly characteristic of increases in alveolar macrophages, neutrophils, T lymphocytes, etc. The cells can secrete a variety of inflammatory mediators, including cytokines, chemokines and growth factors [18, 19]. Inhaled glucocorticoids can inhibit the generation of a variety of inflammatory cytokines and activation of inflammatory cells, thereby reducing airway inflammation. In the present study, after treatment, the levels of IL-8 and TNF-α in BALF were lower in the experimental group than in the control group, indicating that salmeterol-fluticasone in combination with thymopentin had a better inhibitory effect on airway inflammation in patients with moderate to severe COPD, which is similar to the results reported by Christenson et al. [20].

It is widely recognized that immunomodulator thymopentin can regulate cellular immunity. For example, it induces maturation and differentiation of T cells, promotes development of T lymphocyte subsets, and stimulates proliferation of NK cells [21].

However, the effect of thymopentin on humoral immunity of the patients has never been reported. IgE is an immunoglobulin in the body, it activates mast cells, promotes aggregation of eosinophils, and stimulates release of inflammatory cytokines, thereby aggravating airway obstruction and impairing pulmonary function. In the present study, the serum IgE level of the experimental group after treatment was lower than control group, suggesting that salmeterol-fluticasone plus thymopentin significantly improved the humoral immunity in patients with moderate to severe COPD. Quality of life and exercise tolerance are decreased in patients with COPD [22]. The SGRQ is a commonly-used questionnaire to assess quality of life in patients with respiratory diseases, and it consists of 3 domains: respiratory symptoms, disease impacts and activity ability. In the present study, the score for all domains of the SGRQ after treatment was lower in the experimental group than in the control group, implying that the combination therapy of salmeterol-fluticason and thymopentin significantly improves quality of life in patients with moderate and severe COPD.

However, the number of samples is limited in the present study, so more multi-center studies with larger sample sizes are required to explore the exact mechanisms for the efficacy of thymopentin in patients with moderate or severe COPD.

In conclusion, the combination of salmeterol-fluticason and thymopentincan significantly inhibited airway inflammation, and improved humoral immunity, pulmonary function and safety in patients with moderate to severe COPD.

Disclosure of conflict of interest

None.

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