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

Shuyue Li¹*, Qifang Zhu²*, Lei Zhang³, Pengfei Xu⁴, Jifei Geng⁵, Yiming Dong⁶

¹Department of Respiratory Medicine, The Second Hospital of Liao Cheng Affiliated to ShanDong First Medical University, LiaoCheng, ShanDong Province, China; ²Department of Internal Medicine, Shandong University Qilu Hospital High-tech District Hospital, Jin’an, ShanDong Province, China; ³Department of Respiratory Medicine, Linyi County People’s Hospital, ShanDong Province, China; ⁴Department of Pharmacy, Weifang City Yidu Central Hospital, Weifang, ShanDong Province, China; ⁵Department of Internal Medicine, Tai’an Traditional Chinese Medicine Hospital, Tai’an, ShanDong Province, China; ⁶Department of Respiratory Medicine, Weifang People’s Hospital, Weifang, ShanDong Province, China. *Equal contributors and co-first authors.

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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 (FEV₁), forced vital capacity (FVC), the ratio of FEV₁ to FVC, and percentage of FEV₁ as predicted (FEV₁ % 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 composed 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 (FEV₁) to forced vital capacity (FVC) of less than 70%, the percentage of FEV₁ as predicted (FEV₁ % 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 moderate 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 for injection (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 regimens 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
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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 FEV₁ were tested by a spirometer (BTL-08 SPIRO, purchased from Zhangqiu Shunze Bioengineering, and imported from the UK). The ratio of FEV₁ to FVC and FEV₁ % 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, version 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).

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n=71)</th>
<th>Experimental group (n=71)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markedly effective</td>
<td>22 (30.98)</td>
<td>41 (57.75)</td>
<td>10.23</td>
<td>0.001</td>
</tr>
<tr>
<td>Effective</td>
<td>38 (53.52)</td>
<td>27 (38.05)</td>
<td>3.433</td>
<td>0.064</td>
</tr>
<tr>
<td>Ineffective</td>
<td>11 (15.49)</td>
<td>3 (4.23)</td>
<td>5.071</td>
<td>0.024</td>
</tr>
<tr>
<td>Overall effective rate</td>
<td>60 (84.51)</td>
<td>68 (95.77)</td>
<td>5.071</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Note: BMI: body mass index; FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity; FEV₁ % pred: percentage of FEV₁ as predicted; COPD: chronic obstructive pulmonary disease.

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-
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Comparison of airway inflammation between the two groups before and after treatment (X ±s) μg/L

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

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

Comparison of allergen IgE between the two groups before and after treatment (X ±s) U/mL

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n=71)</th>
<th>Experimental group (n=71)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>1395.60±116.50</td>
<td>1434.07±136.91</td>
<td>1.803</td>
<td>0.074</td>
</tr>
<tr>
<td>After treatment</td>
<td>1331.05±98.57***</td>
<td>1138.09±77.78***</td>
<td>11.847</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

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.
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Table 5. Comparison of pulmonary function between the two groups before and after treatment (X ±s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n=71)</th>
<th>Experimental group (n=71)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>1.60±0.44</td>
<td>1.61±0.51</td>
<td>0.125</td>
<td>0.901</td>
</tr>
<tr>
<td>After treatment</td>
<td>1.78±0.51</td>
<td>2.30±0.60***</td>
<td>5.564</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC (L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>2.33±0.43</td>
<td>2.41±0.51</td>
<td>1.011</td>
<td>0.314</td>
</tr>
<tr>
<td>After treatment</td>
<td>2.69±0.40***</td>
<td>2.90±0.48***</td>
<td>2.832</td>
<td>0.005</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>64.59±4.13</td>
<td>65.04±4.22</td>
<td>0.642</td>
<td>0.522</td>
</tr>
<tr>
<td>After treatment</td>
<td>75.48±5.10***</td>
<td>90.59±4.30***</td>
<td>19.086</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁% pred</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>40.59±5.39</td>
<td>41.17±5.84</td>
<td>0.615</td>
<td>0.54</td>
</tr>
<tr>
<td>After treatment</td>
<td>43.08±6.30*</td>
<td>49.70±6.60***</td>
<td>6.114</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity; FEV₁% pred: percentage of FEV₁ 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 (X ±s)

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

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 (%))

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n=71)</th>
<th>Experimental group (n=71)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>2 (2.82)</td>
<td>1 (1.41)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>2 (2.82)</td>
<td>2 (2.82)</td>
<td>0.257</td>
<td>0.612</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (8.45)</td>
<td>1 (1.41)</td>
<td>2.404</td>
<td>0.121</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3 (4.23)</td>
<td>0 (0.00)</td>
<td>1.362</td>
<td>0.243</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>2 (2.82)</td>
<td>1 (1.41)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Overall adverse events</td>
<td>15 (21.13)</td>
<td>5 (7.04)</td>
<td>5.82</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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 a β2 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
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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 characterized 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-fluticasone 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-fluticasone and thymopentin can significantly inhibit airway inflammation, and improved humoral immunity, pulmonary function and safety in patients with moderate to severe COPD.

Disclosure of conflict of interest

None.

Address correspondence to: Yiming Dong, Department of Respiratory Medicine, Weifang People’s Hospital, No. 151 Guangwen Street, Kuiwen District, Weifang 261000, Shandong Province, China. Tel: +86-0536-2930646; Fax: +86-0536-2930646; E-mail: dongyiming37uh@163.com

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