Effect of Corbrin Capsule combined with routine western medicine on the airway remodeling process in patients with stable COPD

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Objective: To explore the effect of Corbrin Capsule combined with routine western medicine on the airway remodeling process in patients with stable COPD. Methods: A total of 120 patients with stable COPD who were treated in the hospital between May 2014 and December 2016 were collected and divided into control group and observation group according to the random number table method, 60 cases in each group. The control group received routine western medicine treatment, and the observation group received Corbrin Capsule combined with routine western medicine treatment. The differences in serum levels of inflammatory factors, growth factors and fibrosis indexes were compared between the two groups before and after treatment. Results: Before treatment, difference in serum levels of inflammatory factors, growth factors and fibrosis indexes were not statistically significant between the two groups of patients. After 8 weeks of treatment, serum IL-2, IL-4, IL-8, IL-18, VEGF, b-FGF, NGF, LN, HA, PⅢNP and C-Ⅳ levels of both groups of patients were significantly lower than those before treatment, and serum IL-2, IL-4, IL-8, IL-18, VEGF, b-FGF, NGF, LN, HA, PⅢNP and C-Ⅳ levels of observation group were lower than those of control group. Conclusion: Corbrin Capsule combined with routine western medicine treatment can effectively inhibit the fibrosis process in patients with stable COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common clinical chronic diseases of the respiratory system with a large number of patients and high mortality, which has become one of the highly concerned public health problems. Ventilation/gas exchange function of patients in stable stage can satisfy patients’ normal need, but there are also studies that have shown that there is still progressive airway remodeling in patients in this period, and the long-term airway function may drop continuously[1-2]. Airway remodeling is the main pathological change of COPD and also the most important link that decides the prognosis of disease[3], and conventional bronchodilator inhalation or oral aminophylline can’t hold the progress, so now many scholars have proposed adjuvant Corbrin Capsule therapy for patients with stable COPD. Corbrin Capsule is a Chinese patent drug that tonifies the lungs and kidney, boosts vital essence and so on, it can be used in the cough and asthma caused by lung-kidney vacuity[4,5], and at present, there is not much research about its effect airway remodeling in patients with stable COPD. In the study, Corbrin Capsule combined with regular western medicine was used to treat patients with stable COPD, and its application value was judged from three airway remodeling-related links of inflammatory cytokines, growth factors and fibrosis, now reported as follows.

2. Information and methods

2.1 Inclusion and exclusion criteria

Inclusion criteria: (1) in accordance with diagnostic criteria for COPD, with GOLD lung function below class III, and with stable disease; (2) receiving regular western medicine treatment for 6
months; (3) cooperating with the treatment all the way. Exclusion criteria: (1) with history of Corbrin Capsule use, or allergic to Corbrin Capsule; (2) complicated by acute or chronic pneumonia; (3) combined with severe heart, liver and kidney insufficiency; (4) combined with malignant tumor disease; (5) with lung function in stage IV or combined with respiratory failure; (6) those complicated by mental illness, severe neurological deficiency or other causes that couldn’t cooperate with the researchers; (7) those with airway limitation caused by bronchiectasis, cystic fibrosis, active pulmonary tuberculosis or other diseases; (8) combined with immune system disease or receiving immunosuppressor recently.

2.2 Case information

A total of 120 patients with stable COPD who were treated in the hospital between May 2014 and December 2016 were collected, signed the informed consent and were then divided into control group and observation group according to the random number table method, 60 cases in each group. Control group included 32 men and 28 women that were 49-75 years old; observation group included 31 men and 29 women that were 50-73 years old. The differences in the gender and age distribution were not significant between the two groups (P>0.05), and the hospital ethics committee approved the study.

2.3 Therapy

Control group of patients received clinical routine western medicine treatment for patients with stable COPD, patients with pulmonary function grade I and II were given one inhalation of salbutamol sulfate (GLAXO WELLCOME, S.A. 100 ug/inhalation, approved by J20110040), 2 times/d; patients with pulmonary function grade III were given one inhalation of budesonide/formoterol (AstraZeneca 160 micrograms/4.5 micrograms/inhalation, imported drug registration number H20140458), 2 times/d as well as oral administration of aminophylline (Kaifeng Pharmaceutical Co., Ltd., drug registration number H20140458), 2 times/d as well as oral administration of aminophylline (Kaifeng Pharmaceutical Co., Ltd., approved by H41022975), etc., for continuous 8 weeks of treatment. Observation group of patients, on the basis of conventional western medicine therapy, received combined Corbrin Capsule treatment, approved by Z10910036), specifically as follows: Corbrin Capsule (Hangzhou Sino-US East China Pharmaceutical Co., Ltd., approved by Z10910036), taken orally, 5 capsules/time, 3 times/d, for continuous 8 weeks of treatment. Western medicine treatment was the same as that of the control group.

2.4 Airway remodeling–related indexes

Before treatment and after 8 weeks of treatment, 5.0 mL fasting cubital venous blood was extracted from two groups of patients, anti-coagulated, then let stand at room temperature for stratification and centrifuged at low speed to get upper serum, which was frozen in -70 ℃ environment for test. Enzyme-linked immunosorbent assay (ELISA) was used to detect the contents of inflammatory factors in it, including interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-8 (IL-8) and interleukin-18 (IL-18). ELISA was used to determine the serum contents of growth factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF) and nerve growth factor (NGF). Chemiluminescence method was used to determine the serum contents of fibrosis indexes, including laminin (LN), hyaluronic acid (HA), N-terminal propeptide of procollagen type III (PIIINP) and collagen type IV (C-IV).

2.5 Statistical processing

Inflammatory factors, growth factors, fibrosis indexes and other measurement data were in terms of mean ± standard deviation, and the comparison was by t test. Statistical software was SPSS24.0 and statistics P<0.05 meant statistical significance in differences.

3. Results

3.1 Inflammatory factors IL-2, IL-4, IL-8 and IL-18 levels

Comparison of serum inflammatory factors IL-2, IL-4, IL-8 and IL-18 levels between two groups of patients before and after treatment was as follows: before treatment, serum IL-2, IL-4, IL-8 and IL-18 levels were not statistically different between the two groups of patients (P>0.05). After 8 weeks of treatment, serum IL-2, IL-4, IL-8 and IL-18 levels of all groups of patients were significantly lower than those before treatment (P<0.05), and serum IL-2, IL-4, IL-8 and IL-18 levels of observation group were significantly lower than those of control group (P<0.05), shown in Table 1.

### Table 1.

Changes in serum IL-2, IL-4, IL-8 and IL-18 levels before and after treatment (pg/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>IL-2</th>
<th>IL-4</th>
<th>IL-8</th>
<th>IL-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>60</td>
<td>Before treatment</td>
<td>1.64±0.28</td>
<td>1.37±0.15</td>
<td>29.37±3.52</td>
<td>193.27±25.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 8 weeks of treatment</td>
<td>0.95±0.16</td>
<td>0.92±0.15</td>
<td>17.62±2.17</td>
<td>114.62±15.23</td>
</tr>
<tr>
<td>Observation group</td>
<td>60</td>
<td>Before treatment</td>
<td>1.63±0.24</td>
<td>1.34±0.18</td>
<td>29.41±3.46</td>
<td>192.63±22.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 8 weeks of treatment</td>
<td>0.42±0.06</td>
<td>0.36±0.05</td>
<td>9.73±1.05</td>
<td>60.81±7.64</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, P<0.05; compared with control group after 8 weeks of treatment, *P<0.05.
were not statistically different between the two groups of patients (P > 0.05). After 8 weeks of treatment, serum VEGF, b-FGF and NGF levels of both groups of patients were significantly lower than those before treatment (P<0.05), and serum VEGF, b-FGF and NGF levels of observation group were significantly lower than those of control group (P<0.05), shown in Table 2.

### 3.2 Growth factors VEGF, b-FGF and NGF levels

Comparison of serum growth factors VEGF, b-FGF and NGF levels between two groups of patients before and after treatment was as follows: before treatment, serum VEGF, b-FGF and NGF levels were not statistically different between the two groups of patients (P > 0.05). After 8 weeks of treatment, serum VEGF, b-FGF and NGF levels of both groups of patients were significantly lower than those before treatment (P<0.05), and serum VEGF, b-FGF and NGF levels of observation group were significantly lower than those of control group (P<0.05), shown in Table 2.

### 3.3 Fibrosis indexes LN, HA, P|[||]NP and C-|V| levels

Comparison of serum fibrosis indexes LN, HA, P|[||]NP and C-|V| levels between two groups of patients before and after treatment was as follows: before treatment, serum LN, HA, P|[||]NP and C-|V| levels were not statistically different between the two groups of patients (P > 0.05). After 8 weeks of treatment, serum LN, HA, P|[||]NP and C-|V| levels of both groups of patients were significantly lower than those before treatment (P<0.05), and serum LN, HA, P|[||]NP and C-|V| levels of observation group were significantly lower than those of control group (P<0.05), shown in Table 3.

### 4. Discussion

The disease evolution trend in patients with stable COPD has been the focus of the clinical research, previous literature believed that airway- related pathological changes in patients in the stage can remain relatively stagnant after the regular symptomatic drug treatment, but the latest studies have shown that pure bronchodilator and other drug maintenance treatment cannot reverse the airway remodeling process in patients with COPD[6,7]. Airway remodeling is based on airway inflammation, the repeated acute inflammation attack - repair - re-injury - re-repair process in airway epithelium results in tissue hyperplasia, which is characterized by irreversible/poor reversible airway ventilation dysfunction and airway hyperresponsiveness. The continuously aggravating airway remodeling process is the core mechanism of the progress of COPD, and therefore, many scholars recommend the Chinese patent medicine Corbrin Capsule therapy for patients with stable COPD[8,9]. The main component of Corbrin Capsule is fermented cordyceps militaris glucose, it has the effects such as nourishing lung Yin as well as relieving cough and reducing sputum, and modern pharmacology proves that it also has the effects such as immunoregulation, anti-inflammation and anti-fibrosis, and is suitable for the treatment of patients with COPD. In this study, Corbrin Capsule was used in the adjuvant treatment of patients with stable COPD, and its influence on patients' airway remodeling process was discussed.

Repeated acute inflammatory attacks are the initial cause of airway remodeling, and the degree of systemic inflammation in patients with COPD can also indirectly reflect the state of airway remodeling[10]. IL-2, IL-4, IL-8 and IL-18 are the typical pro-inflammatory factors that are mainly secreted by mononuclear macrophages, and can form local and systemic inflammatory state, prompt airway secreta generation and induce neutrophil to gather in local lesions[11,12]. In the study, the serum levels of above inflammatory cytokines were first compared between the two groups, and it was found that compared with those before treatment, serum IL-2, IL-4, IL-8 and IL-18 levels of both groups decreased after 8 weeks treatment; further compared with the control group, the observation group were with lower serum IL-2, IL-4, IL-8 and IL-18 levels after 8 weeks of treatment, confirming that Corbrin Capsule combined with conventional western medicine drugs can effectively inhibit the systemic inflammatory response in patients with stable COPD, which is a manifestation of relieved airway remodeling.

The abnormal high expression of multiple growth factors in serum is directly involved in the proliferation of airway epithelial cells, the regeneration of blood vessels and the increase of vascular permeability. The combination of VEGF and its receptor can promote the synthesis of macrophages, mast cells, neutrophils, and so on, which can contribute to airway smooth muscle cell proliferation[13]. b-FGF is a kind of cell mitosis that plays an important role in regulating cell proliferation and differentiation, and study has demonstrated that b-FGF is involved in airway remodeling.
by promoting the proliferation of mast cells[14]. NGF is a nerve growth factor secreted by the bronchial alveolar macrophages, which can help to accelerate the differentiation, growth and chemotaxis of neutrophils[15]. In this study, serum levels of these growth factors were compared between two groups of patients before and after treatment, and it was found that compared with those before treatment, serum VEGF, b-FGF and NGF levels of both groups reduced after treatment; further compared with control group, the observation group werewith lower serum VEGF, b-FGF and NGF levels after treatment, confirming that Corbrin Capsule combined conventional western medicine drug treatment of stable COPD can effectively inhibit airway epithelial cell proliferation and delay the process of airway remodeling.

Airway remodeling is the fibrosis process of airway epithelial tissue, and the abnormal expression of various fibrosis indicators is involved in it. LN, HA, PI[1]NP and C-IV are the recognized fibrosis-related indicators in different studies, their high expression is directly involved in structure change and vascular diameter thickening of airway software tissue, and is the most direct cause of the airway remodeling, and their contents can quantitatively judge airway remodeling severity[16,17]. In this study, serum levels of above fibrosis indexes were compared between two groups of patients before and after treatment, and it was found that compared with those before treatment, serum LN, HA, PI[1]NP and C-IV levels of both groups were lower after treatment; further compared with control group, the observation group were with lower serum LN, HA, PI[1]NP and C-IV levels after treatment, confirming that Corbrin Capsule combined with conventional western medicine drug treatment can effectively inhibit the airway remodeling in patients with stable COPD.

As a result, it can draw the conclusion that Corbrin Capsule combined with conventional western medicine treatment of patients with stable COPD can inhibit the airway remodeling process from reducing inflammatory reaction, inhibiting growth factor and fibrosis index expression and other ways, it is an ideal combination scheme, and it is worthy of popularization and application in clinical practice in the future.

References


