Effect of combined application of tiotropium and Salmeterol and fluticasone propionate powder on disease control in stable COPD patients

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ABSTRACT

Objective: To analyze the effect of combined application of tiotropium and salmeterol and fluticasone propionate powder on disease control in stable COPD patients. Methods: A total of 116 cases of COPD patients who received treatment in our hospital from September 2012 to June 2015 were included in the research and confirmed to be in stable phase according to relevant detection. According to different treatment methods they received, all included subjects were divided into observation group 58 cases and control group 58 cases. Control group received clinical conventional treatment, observation group received combined treatment of tiotropium and salmeterol and fluticasone propionate powder, and then the levels of illness-related indicators in serum and induced sputum were compared between two groups after treatment. Results: γ-GCS, MIP-1α, 8-iso-PGF2, HMGB1, IL-17 and Hdb-2 values in induced sputum of observation group after treatment were lower than those of control group while SP-A value was higher than that of control group; FEF25%-75%, FEV1%, V25 and MMFR values of observation group after treatment were higher than those of control group while serum CXCR3 and CXCL10 values were lower than those of control group; serum copeptin, desmosine, CCL18, CC16 and ANG2 values of observation group after treatment were lower than those of control group. Conclusion: Combined treatment of tiotropium and salmeterol and fluticasone propionate powder for stable COPD patients helps to further stabilize patients’ condition and improve the prognosis.

1. Introduction

Stable chronic obstructive pulmonary disease (COPD) patients’ airway function and local inflammation are both in a certain safe range, but the COPD patients already have airway anatomic change, and can have acute onset in cases of pathogen infection or patients’ weakened constitution, leading to deterioration[1,2]. The treatment of patients with stable COPD is currently the focus of the clinical study, and most scholars believe that stable phase should still be given positive intervention to optimize patients’ condition and reduce the frequency of acute attack. Both tiotropium and salmeterol and fluticasone propionate powder are the main drugs in the clinical treatment of COPD, tiotropium, as anticholinergic drugs, can effectively dilate the airway, and salmeterol and fluticasone propionate powder is the compound preparation of β2 receptor agonist and inhaled corticosteroid, with the effect of both dilating the airway and inhibiting inflammation[3]. In the research, the effect of combined application of tiotropium and salmeterol and fluticasone propionate powder on disease control in stable COPD patients was mainly analyzed, hereby reported as follows.

2. Information and methods

2.1 General information

A total of 116 cases of COPD patients who received treatment in
our hospital from September 2012 to June 2015 were included in the research and confirmed to be in stable phase according to relevant detection. According to different treatment methods they received, all included subjects were divided into observation group 58 cases and control group 58 cases. Control group included 32 male cases and 26 female cases, they were 45-73 years old, the average was (63±7) years old, the course of disease was 5-11 years and the average was (7.28±0.69) years; observation group included 30 male cases and 28 female cases, they were 43-71 years old, the average was (63±7) years old, the course of disease was 6-12 years and the average was (7.83±0.75) years. Differences in baseline information were not significant between two groups (P>0.05), and can be subsequently compared.

2.2 Clinical treatment

Both groups received symptomatic treatment such as oxygen uptake, relieving cough and reducing sputum as well as anti-infection, control group received tiotropium treatment; tiotropium 18 μg, inhaled once every day before sleep. Observation group received combined treatment of tiotropium and salmeterol and fluticasone propionate powder: salmeterol and fluticasone propionate powder 50 μg/time, inhaled every day before sleep. The usage and dosage of tiotropium were the same as that of control group, 4 weeks as a course of treatment.

2.3 Observation indicators

15 d after treatment, 5 mL peripheral venous blood was drawn from patients and centrifuged (4 000 r/min) for 5 min, and then supernatant was collected and frozen-saved at -70 °C. 5ml induced sputum was obtained, processed with 0.1% dithiothreitol, shaken and centrifuged, and then supernatant was collected and also frozen-saved at -70 °C.

Induced sputum-related indicators were detected: glutamyl cysteine synthetase (γ-GCS), macrophage inflammatory protein-1 (MIP-1), 8-iso-prostaglandin F2α (8-iso-PGF2α), high mobility group protein Bi (HMGB1), interleukin-17 (IL-17), surfactant protein A (SP-A) and human-β-defensin-2 (Hbd-2).

Small airway function-related indicators: forced expiratory volume in 1 second (FEV1), maximal mid-expiratory flow rate (MMFR), FEF25%-75%, peripheral blood mononuclear cell CXC chemokine receptor 3 (CXCR3) and interferon-γ -induced protein-10 (CXCL10).

Serum illness-related indicators: copeptin, desmosine, chemokine CCL18, Clara cell secretory protein CC16 (CC16) and angiopoietin 2 (ANG2).

2.4 Statistical methods

Data obtained in the research was analyzed by SPSS 23.0 software, measurement data was in terms of Mean ± SD, comparison between two groups was by t test and P<0.05 was set as the standard of statistical significance in differences.

3. Results

3.1 Induced sputum-related indicators

Induced sputum is from the deep airway, can directly reflect the levels of inflammation and lesion-related indicators in local lesion, and is currently one of the most common means to judge the illness of COPD patients. In the research, induced sputum was obtained from patients after treatment, γ-GCS, MIP-1α, 8-iso-PGF2 and other recognized factors closely related to the occurrence and development of COPD in it were detected, and results showed that γ-GCS, MIP-1α, 8-iso-PGF2, HMGB1, IL-17 and Hbd-2 values in induced sputum of observation group after treatment were lower than those of control group while SP-A value was higher than that of control group (P<0.05), shown in Table 1.

3.2 Small airway function-related indicators

COPD patients are accompanied with small airway function injury and irreversible airflow limitation, the detection of small airway function-related indicators can effectively reflect airway function and disease severity, and obtained results showed as follows: FEF25%-75%, FEV1%, V25 and MMFR values of observation group after treatment were higher than those of control group while serum CXCR3 and CXCL10 values were lower than those of control group (P<0.05), shown in Table 2.

3.3 Serum illness-related indicators

COPD patients may have changed levels of a series of serum factors, the illness-related factors currently recognized by many studies include copeptin, desmosine, CCL18, CC16, ANG2 and so on, and their fluctuation in the course of COPD may indirectly reflect the degree of disease progress and the effectiveness of treatment. ELISA method was used to detect the levels of above

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>γ-GCS (μg/mL)</th>
<th>MIP-1 (μg/mL)</th>
<th>8-iso-PGF2 (pg/mL)</th>
<th>HMGB1 (ng/L)</th>
<th>IL-17 (ng/mL)</th>
<th>SP-A (ng/mL)</th>
<th>Hbd-2 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>0.11±0.01</td>
<td>0.08±0.01</td>
<td>143.28±12.09</td>
<td>186.23±15.77</td>
<td>41.28±3.82</td>
<td>683.92±65.12</td>
<td>192.73±17.63</td>
</tr>
<tr>
<td>Control</td>
<td>0.18±0.02</td>
<td>0.17±0.02</td>
<td>276.59±23.51</td>
<td>291.56±29.08</td>
<td>69.21±5.97</td>
<td>427.14±66.51</td>
<td>227.51±20.93</td>
</tr>
<tr>
<td>t</td>
<td>5.129</td>
<td>5.093</td>
<td>11.283</td>
<td>13.284</td>
<td>8.293</td>
<td>10.729</td>
<td>11.092</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>FEF25%-75%</th>
<th>FEV1%</th>
<th>V25 (L/s)</th>
<th>MMFR (L/s)</th>
<th>CXCR3 (ng/L)</th>
<th>CXCL10 (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>45.38±4.11</td>
<td>85.28±7.23</td>
<td>1.71±0.13</td>
<td>3.02±0.27</td>
<td>732.83±65.95</td>
<td>165.06±14.28</td>
</tr>
<tr>
<td>Control</td>
<td>34.17±3.05</td>
<td>76.95±7.35</td>
<td>0.98±0.08</td>
<td>2.14±0.23</td>
<td>1047.24±98.77</td>
<td>217.54±20.97</td>
</tr>
<tr>
<td>t</td>
<td>7.932</td>
<td>8.194</td>
<td>5.394</td>
<td>5.783</td>
<td>12.394</td>
<td>8.293</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Comparison of serum illness-related indicator values between two groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Copeptin (μg/L)</th>
<th>Desmosine (ng/mL)</th>
<th>CCL18 (ng/mL)</th>
<th>CC16 (pg/mL)</th>
<th>ANG2 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>0.13±0.01</td>
<td>5.82±0.53</td>
<td>1.58±0.13</td>
<td>0.29±0.02</td>
<td>2.13±0.22</td>
</tr>
<tr>
<td>Control</td>
<td>0.56±0.04</td>
<td>12.69±1.45</td>
<td>2.17±0.23</td>
<td>0.48±0.04</td>
<td>5.07±0.54</td>
</tr>
<tr>
<td>t</td>
<td>5.283</td>
<td>6.982</td>
<td>5.472</td>
<td>6.034</td>
<td>6.723</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

lower than those of control group (P<0.05), shown in Table 3.

4. Discussion

Chronic obstructive pulmonary disease (COPD) is one of the main respiratory system diseases endangering the health of the middle-aged and old, and repeated airway infection and the formation of irreversible airflow limitation are the main pathological changes. After part of COPD patients receives regular treatment and intervention such as smoking cessation and enhanced physique, the disease can be in stable phase. But because airway remodeling and other anatomical changes have occurred, local airway infection can lead to acute outbreak of COPD and rapid deterioration of airflow function, and therefore, stable COPD patients should still strengthen the treatment and intervention in order to prevent disease progression to the largest extent[4, 5]. As a specific selective anticholinergic drug, tiotropium can inhibit the smooth muscle M3 receptor and play the bronchus dilating effect. Salmeterol and fluticasone propionate is the long-acting compound preparation of β2 agonist salmeterol and inhaled corticosteroid fluticasone propionate, salmeterol selectively agitates the β2 adrenergic receptor in airway smooth muscle to dilate bronchi, and fluticasone propionate can act on every link of inflammation and inhibit the formation and activation of inflammatory cells[6]. Tiotropium can significantly improve the clinical symptoms of patients with COPD, but the effect in inhibiting its recurrence is poor, salmeterol and fluticasone propionate can inhibit inflammation so as to reduce acute outbreak of COPD, so some scholars propose that tiotropium is combined applied with salmeterol and fluticasone propionate, which embarks from the different mechanisms to strengthen the control of disease in stable COPD patients. In the research, stable COPD patients were selected as research subjects, tiotropium as well as salmeterol and fluticasone propionate powder were applied in patients in different combinations, and the effect of combined use of the two drugs on patients was mainly analyzed.

γ-glutamine cysteine synthase (γ-GCS) is the rate-limiting enzyme synthesized by glutathione and is one of the important antioxidant enzymes in the body, γ-GCS expression level is associated with neutrophil percentage, and lung function of patients reduces with the increase of γ-GCS level. Macrophage inflammatory protein-1 α (MIP-1 α) belongs to the family of C-C chemokines, its performance is prominent in the inflammatory response, and it can promote inflammatory factor aggregation and increase local airway inflammation. MIP-1 α level is positively correlated with the level of neutrophils in the body and is one of the important factors causing severe COPD[7, 8]. 8-iso-prostaglandin F2 α (8-iso-PGF2 α) is the prostanoïd metabolite discovered in recent years, is produced after free radical damage of the cell membrane and lipid peroxidation, and can directly cause lung damage and airway remodeling. High mobility group protein B1 (HMGB1) is very important late inflammatory mediator in the human body that is produced by stimulation of lipopolysaccharide and various cytokines, and endotracheal administration of exogenous HMGB1 can lead to acute inflammation injury of the lung[9]. Interleukin-17 (IL-17) plays an important role in the chronic inflammation induced by T cells, and studies have shown that there is high expression of IL-17 in the lung tissue and serum of the COPD model rats, which is directly related to the illness severity. Pulmonary surfactant protein A (SP-A) belongs to the pulmonary surfactant-associated proteins, participates in maintaining normal physiological functions of the lung, and plays an important role in maintaining the stability of small airway and reducing airway resistance. SP-A content is positively correlated with the degree of airflow obstruction and small airway function change, and reduced SP-A value is one of the important factors of limited airflow[10]. Human-β-defensin-2 (Hbd-2) is induced and expressed in inflammatory and microbial stimuli, as chemotactic factor, Hbd-2 can increase inflammatory cell recruitment, and when local or systemic obvious inflammatory response occurs, Hbd-2 expression level can increase. Above research results showed that γ-GCS, MIP-1 α, 8-iso-PGF2, HMGB1, IL-17 and Hbd-2 values in induced sputum of observation group after treatment were lower while SP-A value was higher, indicating that under the combined treatment of tiotropium and salmeterol and fluticasone propionate powder, local airway inflammation in COPD patients was improved, and the degree of overall disease severity was reduced.

Small airway lesions and airway remodeling are the core changes of the COPD patients, and inflammatory cell infiltration and smooth muscle hypertrophy in small airway can cause the airway stenosis and airflow limitation. The performance of small airway dysfunction is not significant in the normal pulmonary function test, which is also the important reason for the early missed diagnosis and misdiagnosis of a lot of COPD patients[11]. Research has confirmed that V25 is the reliability index to judge the degree of airflow limitation, and when small airway lesions occur, V25 value decreases significantly. Forced expiratory volume in 1 second (FEV1) is the most common index for clinical judgment of pulmonary dysfunction, but the detection sensitivity is not high, combined detection with the other indicators is required in order to make clear the lesions. Research shows that maximum peak expiratory flow (PEF) can better reflect the MEF50 abnormal rate of children with asthma, and can evaluate the illness severity and guide treatment. In view of the significance of PEF in reflecting airway instability and detecting long-term changes of respiratory disease, many scholars put forward that it is used as one of the conventional indexes to detect the illness in patients with COPD. Maximal mid-expiratory flow rate (MMFR) and FEF25%-75% are both effective indicators to evaluate small airway function, and after exclusion of smoking and environmental interference, it is found that both MFR and FEF25%-75% values in patients with COPD are higher than in patients with typical asthma, but lower than those in normal healthy people, which indicates that patients
with COPD and asthma have a certain degree of small airway dysfunction[12]. Peripheral blood mononuclear cell CXC chemokine receptor 3 (CXCR3) is one member of CXC chemokines family expressed in activated T cells, studies have shown that CXCR3 expressed in CD8+T cells in the lung tissue is positively correlated with disease severity, and with aggravated airway lesions and increased severity of airflow limitation, the level of CXCR3 also rises correspondingly, and is directly involved in the progression of COPD. Interferon-γ-reduced protein-10 (CXCL10) is one of the ligands of CXCR3, study has confirmed that CXCR3 expression level in patients with acute outbreak of COPD is significantly higher than that in patients with stable COPD and is positively proportional to the degree of inflammation, which plays the role of recruiting inflammatory factors to the lesion site and continuing the inflammation state of lung tissue[13]. Above research results showed that FEF25%-75%, FEV1%, V25 and MMFR values of observation group after treatment were higher while serum CXCR3 and CXCL10 values were lower, indicating that the combined treatment of tiotropium and salmeterol and fluticasone propionate powder could significantly improve COPD patients’ small airway function and optimize the illness.

Copeptin is the precursor of antidiuretic hormone that can directly reflect the antidiuretic hormone levels. Stimulating factors such as infection, hypoxia and acidosis can all lead to increased antidiuretic hormone levels, and serum copeptin content also increases accordingly and it can be a COPD biomarker[14]. Desmosine is the characteristic cross-linking amino acid of mature elastin, and helps maintain elastin structure stability. Desmosine in the human body can only be derived from the hydrolysis of elastin, so its content can directly indicate elastin degradation or not. Study shows that desmosine is negatively correlated with FEV1 values in COPD patients, and can be a valid marker to measure pulmonary function in patients with COPD. CCL18 expression is very little in healthy people, CCL18 expression increases when inflammation diseases such as COPD occurs, and the expression levels are different in patients with different severity of COPD, so it is believed that CCL18 can serve as the evaluation index to judge COPD disease severity and prognosis. CC16 can inhibit the expression of inflammatory mediators and thus play strong anti-inflammatory effect. Study shows that CC16 levels rise in patients with COPD, which may be due to the increased reactive CC16 expression caused by high levels of inflammation in patients’ body. CC16 can indirectly reflect the body’s inflammatory state, and evaluate the severity of COPD. Angiopoietin 2 (ANG2) belongs to the angiopoietin family and can damage vascular formation and promote vascular degeneration, research has confirmed that the ANG2 is associated with transplanted lung dysfunction, and ANG2 level changes are involved in the evolution of disease in patients with COPD[15]. Above research results showed that serum copeptin, desmosine, CCL18, CC16 and ANG2 values of observation group after treatment were lower, indicating that the combined treatment of tiotropium and salmeterol and fluticasone propionate powder could further optimize the illness of stable COPD patients.

To sum up, it is concluded as follows: combined treatment of tiotropium and salmeterol and fluticasone propionate powder for patients with stable COPD helps to further stabilize patients’ condition and improve the prognosis, and it’s worth popularization and application in clinical practice in the future.

References