Effect of Ambroxol on the lung function, oxidative stress and inflammatory cytokines in AECOPD patients

Kaisaier Aizezi¹, Xiaokai Maimaitiyimin², Xiao-Hong Yang¹*

¹Department of Respiratory and Critical Care Medicine, The Xinjiang Uygur Autonomous Region people’s Hospital, Urumqi 830001, Xinjiang, China
²Department of Chest Surgery, The Xinjiang Uygur Autonomous Region people’s Hospital, Urumqi 830001, Xinjiang, China

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ABSTRACT

Objective: To explore the effect of Ambroxol on the lung function, oxidative stress and inflammatory factor in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Methods: From February 2014 to August 2015, a total of 90 patients with AECOPD in our hospital were chosen as research objects and divided into observation group and control group according to their admission date with 45 cases in each group. All patients were given conventional treatment, and on this basis the observation group was given Ambroxol for 10 d. Before and after treatment, the lung function indicators (FVC, FEV₁ and FEV₁/FVC), the serum oxidative stress indicators (MDA and SOD) and the serum inflammatory factors (IL-6, IL-10 and TNF-α) were detected and compared, respectively. Results: After treatment, the lung function indicators FEV₁, FVC and FEV₁/FVC in observation group were (1.83 ± 0.25) L, (2.76 ± 0.21) L and (72.29 ± 5.10)% respectively. Compared with before treatment and the post-treatment control group, they were significantly increased; after treatment, the oxidative stress indicator MDA in observation group was (4.24 ± 1.09) nmol/mL, while SOD was (82.20 ± 6.23) Nu/mL. Compared with before treatment and the post-treatment control group, the former was significantly reduced, while the latter was obviously increased; after treatment, the inflammatory factors IL-6 and TNF-α in the observation group were (5.15 ± 1.09) pg/mL and (3.35 ± 0.68) ng/L respectively, while IL-10 was (7.22 ± 1.23) pg/L. Compared with before treatment and the post-treatment control group, the former two were apparently decreased, while the latter one was significantly grown. Conclusion: Ambroxol can obviously reduce the inflammatory response and significantly improve the oxidative stress and lung function in patients with AECOPD, which has positive significances in clinical.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic airway inflammatory disease in clinical, characterized by the airflow limitation. The long-term repeated exacerbation is an important reason for the progression of the disease, which causes reduced lung function and affected quality of life in patients[1-2]. Studies have shown that airway inflammation and oxidative stress are important pathological basis of COPD, and the anti-inflammatory factor/pro-inflammatory factor imbalance and the oxidation/antioxidant imbalance play key roles in the pathogenesis and progression of COPD[3-4]. Ambroxol is a new type of apophlegmatisant, and findings in the previous studies found it not only improved the phlegm clearance and respiratory status in patients with respiratory disease, but also had certain anti-inflammatory and antioxidant activities[5-6]. In this study, the application of Ambroxol in the treatment of AECOPD had achieved satisfactory results, and details as follows.

*Corresponding author: Xiao-Hong Yang, Department of Respiratory and Critical Care Medicine, The Xinjiang Uygur Autonomous Region people’s Hospital, Urumqi 830001, Xinjiang, China. Tel: 13579899442 Email: casel88@163.com Funding: Provincial Research Project of Xinjiang Uygur Autonomous Region (NO. 2014123A166).
2. Materials and methods

2.1. Inclusion and exclusion criteria

(1) In accordance with the diagnostic standards of COPD in the 2013 revised guide for the diagnosis and treatment of chronic obstructive pulmonary disease by the Chinese medical association[7], and the COPD was confirmed by clinical examination, pulmonary function examination and imaging examination; (2) lung function grades at || || were regarded as acute exacerbation of COPD; (3) patients with asthma, bronchiectasis, interstitial lung disease and other chronic lung disease were ruled out; (4) patients with immune system disease, circulatory system disease or liver and kidney function insufficiency were eliminated; (5) pregnant women or lactating women were ruled out; (6) patients who received a surgery or experienced a trauma recently were eliminated; (7) patients who were allergic to drugs were excluded.

2.2. Clinical data

From February 2014 to August 2015, a total of 90 patients with AECOPD from the Department of Respiratory and critical care medicine of the Xinjiang Uygur Autonomous Region people’s Hospital were chosen as research objects and divided into observation group and control group according to their admission date. In the observation group (45 cases), there were 31 males and 14 females, who were 44-82 (62.13 ± 18.92) years old with the course of COPD 4-21 (14.32 ± 8.20) years; Lung function grades: grade || 29 cases and grade ||| 16 cases; there were 15 cases with smoking history. In the control group (45 cases), there were 28 males and 17 females, who were 46-80 (62.45 ± 17.43) years old with the course of COPD 3-20 (13.78 ± 8.05) years; Lung function grades: grade || 30 cases and grade ||| 15 cases; there were 14 cases with smoking history. There were no statistical differences regarding gender, age, lung function grade, course of illness and smoking history between the two groups.

2.3. Therapeutic methods

The two groups both received symptomatic treatment including spasmolysis, relieving asthma, anti-infection, oxygen inhalation and correction of water-electrolyte balance and acid-base balance. On the basis of symptomatic treatment, the observation group was given Ambroxol (Ambroxol Hydrochloride for Injection, Hainan WEICON pharmaceutical co., LTD, approved by the state H20060223). In detail, 15 mg of Ambroxol was added into 100 mL 0.9% sodium chloride injection for intravenous drip twice a day for a 10-day continuous treatment.

2.4. Observation indicators

2.4.1. Lung function before and after treatment

The lung function indicators including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and FEV1/FVC were detected using D-97204 Spirometer (Jaeger company, Germany).

1.4.2. Oxidative stress before and after treatment

3 mL of fasting venous blood was collected and anti-coagulated by heparin, then serum was obtained by centrifugation. The serum levels of superoxide dismutase (SOD) and malondialdehyde (MDA) were measured by chemical colorimetry, and kits were purchased from BIOLEAF (Shanghai) biological technology co., LTD.

1.4.3. Inflammatory factors before and after treatment

3 mL of fasting venous blood was collected and anti-coagulated by heparin, then serum was obtained by centrifugation. The serum levels of interleukin-6 (IL-6), IL-10 and tumor necrosis factor-α (TNF-α) were detected by enzyme linked immunosorbent assay (ELISA), and kits were bought from TONGWEI Reagent (Shanghai) co., LTD.

1.5. Statistics

Data were analyzed using SPSS 19.0 medical statistical software. Measurement data were described as mean ± standard deviation (Mean ± SD), and the inter-group and intra-group comparisons were carried out by t test. The values of P<0.05 were considered to be statistically significant.

3. Results

3.1. The comparison of lung function indicators before and after treatment

After treatment, the lung function indicators FEV1, FVC and FEV1/FVC in observation group were (1.83 ± 0.25) L, (2.76 ± 0.21) L and (72.29 ± 5.10)%, respectively. Compared with before treatment and the post-treatment control group, they were significantly increased (P<0.05); after treatment, the lung function indicators FEV1, FVC and FEV1/FVC in control group were also distinctly increased compared with before treatment (P<0.05).

3.2. The comparison of oxidative stress indicators before and after treatment

After treatment, the oxidative stress indicator MDA in observation group was (4.24 ± 1.09) nmol/mL, while SOD was (82.20 ± 6.23) Nu/mL. Compared with before treatment and the post-treatment control group, the former was significantly reduced, while the latter was obviously increased (P<0.05); after treatment, the oxidative indicator SOD in control group was also significantly increased compared with before treatment (P<0.05).

3.3. The comparison of inflammatory factors before and after treatment

After treatment, the inflammatory factors IL-6 and TNF-α in the observation group were (5.15 ± 1.09) pg/mL and (3.35 ± 0.68) ng/L, respectively, while IL-10 was (7.22 ± 1.23) pg/L. Compared with before treatment and the post-treatment control group, the former two were apparently decreased, while the latter one was significantly grown (P<0.05); after treatment, the inflammatory factors IL-6 and TNF-α in control group were also significantly decreased compared with before treatment (P<0.05).
Table 1.
Table the comparison of lung function indicators before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Time point</th>
<th>FEV₁ (L)</th>
<th>FVC (L)</th>
<th>FEV₁/FVC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>45</td>
<td>Before therapy</td>
<td>1.10 ± 0.23</td>
<td>1.87 ± 0.19</td>
<td>56.65 ± 4.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After therapy</td>
<td>1.83 ± 0.25*#</td>
<td>2.76 ± 0.21*#</td>
<td>72.29 ± 5.10*#</td>
</tr>
<tr>
<td>Control</td>
<td>45</td>
<td>Before therapy</td>
<td>1.11 ± 0.20</td>
<td>1.79 ± 0.18</td>
<td>55.12 ± 4.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After therapy</td>
<td>1.45 ± 0.31*</td>
<td>2.23 ± 0.22*</td>
<td>67.26 ± 5.18*</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, *P<0.05; compared with the post-treatment control group, #P<0.05.

Table 2.
Table 2 the comparison of oxidative stress indicators before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Time point</th>
<th>MDA (nmol/mL)</th>
<th>SOD (Nu/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>45</td>
<td>Before therapy</td>
<td>7.12 ± 2.23</td>
<td>71.32 ± 5.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After therapy</td>
<td>4.24 ± 1.09*#</td>
<td>82.20 ± 6.23*#</td>
</tr>
<tr>
<td>Control</td>
<td>45</td>
<td>Before therapy</td>
<td>7.08 ± 1.87</td>
<td>72.03 ± 4.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After therapy</td>
<td>5.63 ± 1.26</td>
<td>77.43 ± 5.78*</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, *P<0.05; compared with the post-treatment control group, #P<0.05.

Table 3.
Table 3 the comparison of inflammatory factors before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Time point</th>
<th>IL-6 (pg/mL)</th>
<th>TNF-α (ng/L)</th>
<th>IL-10 (pg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>45</td>
<td>Before therapy</td>
<td>20.10 ± 2.65</td>
<td>11.54 ± 9.12</td>
<td>4.69 ± 0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After therapy</td>
<td>5.15 ± 1.09*#</td>
<td>3.55 ± 0.68*#</td>
<td>7.22 ± 1.23*#</td>
</tr>
<tr>
<td>Control</td>
<td>45</td>
<td>Before therapy</td>
<td>18.78 ± 2.23</td>
<td>10.68 ± 2.05</td>
<td>4.47 ± 0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After therapy</td>
<td>11.34 ± 2.04*</td>
<td>7.16 ± 1.53*</td>
<td>5.06 ± 1.00</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, *P<0.05; compared with the post-treatment control group, #P<0.05.

4. Discussion

Although the pathogenesis of COPD has not been fully elucidated, it is found that a variety of inflammatory cells and mediators play an important role in this process with the deepening of the research. Callebaut et al.[8] found that the serum levels of inflammatory cytokines CRP and IL-6 were significantly increased in patients with AECOPD, and they grew greatly with the increase of neutrophils and the enhancement of airflow limitation. It is thought that the airway obstruction could be aggravated due to the airway inflammation induced by the large release of pro-inflammatory factors. Therefore, targeted anti-inflammatory therapy should be taken to treat AECOPD. IL-6 and TNF-α are common pro-inflammatory factors. IL-6 is mainly produced by fibroblasts and the activated T cells, acting as stimulator to promote the growth and differentiation of myeloid progenitor cells in a synergistic way with colony-stimulating factor[9]. TNF-α is an important inflammatory mediator, produced by mononuclear macrophages, and it stimulates the release of inflammatory particles by activating lymphocytes, neutrophils and mast cells. Besides, TNF-α reflects the aggravated lung tissue damage and the slowed inflammatory response in patients with COPD, which are closely associated with the occurrence and development of COPD[10]. IL-10 is a kind of immune suppression anti-inflammatory factor, capable to inhibit the functions of pro-inflammatory mediators such as IL-8, TNF-α and proteolytic enzyme. In addition, it reduces the mRNA stability of IL-8 and IL-6 to exert its anti-inflammatory effect[11].

As a new type of apophlegmatisant, Ambroxol acts with antibiotics to enhance the anti-infective effect and reduce the putum viscosity.

In this study, Ambroxol was used in the treatment of AECOPD, and the results show that not only lung function indicators FEV₁, FVC and FEV₁/FVC were significantly improved, but also the pro-inflammatory factors IL-6 and TNF-α were significantly reduced, and IL-10 was significantly increased after the administration of Ambroxol. More importantly, its effect was superior to the conventional treatment alone. Lung function is an indicator of efficacy for the treatment of COPD, and this study found that Ambroxol was not only beneficial to improve the curative effect, but also helped to correct the pro-inflammatory factor/anti-inflammatory factor imbalance, reducing inflammatory response. This may be explained by the reduced airway serosity and the formation of mucinous liquids, thus the cilia movement and lysis of sticky secretions were enhanced to promote the clearance of sticky sputum, thus to keep the respiratory tract unobstructed and improve the airway mucosa damage, resulting in decreased release of inflammatory cytokines to reduce the inflammation and continuously improve the lung function[12-14].

Study found that oxidative stress is one of the pathogenesis of COPD mechanisms, mainly featured by oxidation/anti-oxidation imbalance. When oxidants increase and/or anti-oxidants decrease, the oxidative stress is enhanced[15]. Oxidative stress causes lipid peroxidation, leading to the decrease of anti-protease activity and the increase of mucus secretion. As a result, the airway epithelium and the lung tissue go through chronic damage, and inflammation is further aggravated to promote the progress of COPD. MDA is the main product of lipid peroxidation, and SOD is the scavenger for superoxide anion free radical with the ability to remove oxygen free...
radicals, to inhibit cellular damage and apoptosis, which is a sensitive indicator of the body's antioxidant power. Ka mierczak et al found the imbalance existed in patients with COPD, with significantly increased serum level of MDA and significantly decreased SOD[16]. This study further observed the effect of Ambroxol on the oxidative stress indicators in patients with AECOPD, and results demonstrated that MDA was obviously decreased, while SOD was apparently increased in the observation group treated by Ambroxol compared with before treatment and the post-treatment control group ($P<0.05$), indicating Ambroxol could improve the oxidative stress for patients with AECOPD. The possible explanations account for this induced by Ambroxol may include[17-20]: (1) the pre-oxidative metabolism of inflammatory cells is reduced; (2) the clearance of mucous is promoted; the lysis of polysaccharide fiber of glycoproteins is accelerated; the number of lymphocytes and macrophages is reduced; the discharge oxidation metabolites is speeded and the local oxidation level is improved; (3) the normal status of pulmonary alveoli is maintained, and the activating reaction of IgG is inhibited; (4) Ambroxol works with anti-inflammatory drugs or antioxidants to effectively remove the free radicals in the body.

To sum up, Ambroxol can obviously reduce the inflammatory response and significantly improve the oxidative stress and lung function in patients with AECOPD, which has positive significances in clinical.

References


