Original Article
The effect of adjuvant therapy with ambroxol hydrochloride in elderly chronic obstructive pulmonary disease patients

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Abstract: Objective: To investigate the influence of adjuvant therapy with ambroxol hydrochloride (ABH) on the clinical symptoms and pulmonary function of elderly chronic obstructive pulmonary disease (COPD) patients. Methods: From September 2018 to September 2019, 142 elderly COPD patients admitted to the Affiliated Hospital of Hebei University were recruited as the research cohort. Based on different treatment method each patient underwent, they were assigned to the control group (CG, n=69) or the research group (RG, n=73). In the CG, the patients were treated with routine symptomatic treatment, and the patients in the RG were treated with ABH in addition to the treatment administered in the control group. Results: After the therapy, the clinical symptom scores in the RG were significantly lower than they were in the CG (P<0.05), and the total effective rate of the clinical treatment was significantly higher than it was in the CG (P<0.05). The 6MWT scores in the RG were higher than they were in the CG (P<0.001), and the CAT scores were significantly lower than they were in the CG (P<0.001). The inflammatory factor levels in the RG were markedly lower than they were in the CG (P<0.001), and the pulmonary function and immune function indexes were better than they were in the CG (P<0.05). There was no significant difference in the adverse effects between the two groups (P>0.05). Conclusion: ABH can effectively relieve the clinical symptoms and improve the pulmonary function of elderly COPD patients, with a significant clinical effectiveness and high drug safety, so it is worthy of promoting.

Keywords: Chronic obstructive pulmonary disease, ambroxol hydrochloride, clinical symptoms, lung function, curative effect

Introduction

COPD is a heterogeneous and multi-system disease. The air in the lungs is difficult to discharge due to the narrowing of the respiratory tract, and COPD’s morbidity and mortality are on the rise [1, 2]. COPD affects about 300 million people all over the world. Air pollution is the main risk factor of COPD, and 3 billion people are in this dangerous environment [3], which has caused a huge burden to the medical and health systems [4]. With the increasing aging of the domestic population, COPD has been prevalent in the elderly population and has become a major public health problem [5]. However, most chronic respiratory burdens can be prevented and improved by treatment [6], so it is of great significance to seek effective treatment methods.

Dyspnea is a common symptom of patients with COPD, and it leads to limited activity and decreased motor function, and it affect patients’ psychology and quality of life, so it needs effective intervention [7]. Drug therapy and smoking cessation are the main treatment measures, and some patients can be considered for lung rehabilitation, long-term oxygen therapy, and surgery [8]. Inhalation bronchodilators are the main treatment for COPD at present [9, 10]. However, bronchodilators are bound up with an increased risk of severe cardiovascular disease, they are expensive, and many patients still develop symptoms after treatment [11, 12]. ABH is a new active metabolite of bromhexine, and it can specifically bind to lung tissue, stimulate phospholipid synthesis, promote the production and secretion of pulmonary surfactants, reduce lung injuries, alleviate...
inflammatory reactions, and dissolve sputum [13]. ABH is widely used in the clinical therapy of respiratory distress syndrome (RDS) due to its simple operation, low cost, and high safety [14, 15]. However, there is a lack of clinical research on the therapeutic effect of ABH in COPD, so its clinical effectiveness in COPD is still unclear.

Therefore, this research was designed to treat elderly COPD patients with ABH and to investigate its ability to improve their clinical symptoms and lung function.

Clinical data and methods

Collection of the patients’ clinical data

From September 2018 to September 2019, 142 elderly patients with COPD admitted to Affiliated Hospital of Hebei University were recruited as the research cohort. Based on different treatment methods each patient underwent, they were divided into the CG (n=69) or the RG (n=73). In the CG, the patients were treated with the routine symptomatic treatment, and the patients in the RG were treated with ABH in addition to the routine symptomatic treatment.

Inclusion criteria: All the patients were diagnosed with COPD, and the diagnostic criteria were based on the relevant guidelines in 2017 [16]; All the patients were ≥65 years old, their clinical data were complete, they had not been treated with bronchiectasis drugs in the previous month, and they had not taken any anti-infective medication for nearly two weeks. The patients and their dependents were informed of the study and signed the informed consent.

Exclusion criteria: Patients allergic to the drugs used in this study, patients comorbid with malignant tumors, other lung diseases, liver or kidney insufficiency, diabetes, or hypertension, patients with communication barriers and patients with poor compliance.

This research was approved by the Medical Ethics Committee of the Affiliated Hospital of Hebei University.

Therapeutic methods

In the CG, the patients were treated with routine therapy. The patients were given symptomatic treatment such as oxygen uptake, antitussives, antiasthmatics, antinflectives, and the correction of water and electrolyte disorders according to their condition. In addition to the treatment administered to the CG, the patients in the RG were also administered an intravenous infusion of ABH (Hebei Ideal & Hightech Pharmaceutical Co., Ltd., SFDA Approval no. H20113062), 90 mg/time, twice a day. In both groups, the patients were treated for 14 days.

Measurement methods

Serum inflammatory factors: Before and after the therapy, 5 ml of fasting venous blood was drawn from all the patients, stored at room temperature for 30 min and centrifuged at 3000×g at 4°C for 10 min. Then, the supernatant was obtained and stored in a freezer at -80°C for later examination. Enzyme-linked immunosorbent assays (ELISA) were used to test the serum IL-6, IL-8, and TNF-α levels. The kits were provided by Wuhan Moshake Biotechnology Co., Ltd., and the operation was carried out strictly in accordance with the specifications. The absorbance (OD value) was measured with an enzyme-labeling instrument at a wavelength of 450 nm, and the corresponding concentration was converted from the standard line.

Lung function indicators: Before and after the therapy, the peak expiratory flow rate (PEF), the forced expiratory volume in one second (FEV1), and °C forced vital capacity (FVC) were measured using the chest lung function tester HI801.

Immune function indexes: Before and after the therapy, the CD3+, CD4+ and CD8+ levels were tested using flow cytometry (Flow Cytometer, ACEA Biosciences, the States).

Outcome measures

The main outcome measures: Clinical symptom scores were used to evaluate the improvement in the clinical symptoms in both groups, and the evaluation criteria are shown in Table 1. The clinical effectiveness was analyzed in both groups, and the efficacy evaluation criteria are shown in Table 2. The changes in the pulmonary function (pulmonary function indexes: PEF, FEV1, and FVC) were observed before and after the therapy.
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Secondary outcome measures: The six-minute walking test (6MWT) [17] and the COPD assessment test (CAT) [18] were used to evaluate the conditions of the patients in both groups. Before and after the therapy, the changes in the serum inflammatory factor levels (IL-6, IL-8 and TNF-α) and the immune function (immune function indicators: CD3+, CD4+ and CD8+ of T lymphocytes) were observed in both groups.

Statistical analysis

In this research, SPSS 23.0 (SPSS Co., Ltd., Chicago, USA) was used to analyze the collected data statistically. GraphPad Prism 8 (GraphPad Software Co., Ltd., San Diego, United States) was used to draw the figures of the collected data. The enumeration data were expressed as percentages (%), tested using chi-square tests and represented as $\chi^2$. The quantitative data were represented as the mean ± standard deviation ($\pm$). Independent samples t-tests were used for the comparisons between the two groups, which were expressed by T. P<0.05 indicated a significant difference.

Results

Basic information of patients

By collecting the patients’ baseline data in both groups, we found that there were no significant differences in terms of age, gender, BMI, course of the disease, stage, dust contact history, smoking history, alcoholism history, or place of residence between the two groups (P>0.05), so they were comparable (Table 3).

Improvement of the clinical symptoms

The clinical manifestations and sign scores were used to evaluate the improvement in the clinical symptoms in both groups after the therapy. The results indicated that there was no significant difference in the scores between the two groups before the therapy (P>0.05). After the therapy, the sign scores in both groups were lower than they were before the therapy (P<0.001), and the scores in the RG were markedly lower than they were in the CG (P<0.001) (Figure 1).

Comparison of the clinical efficacy

By evaluating the clinical efficacy in both groups, it was found that the overall effective rate of the clinical treatment in the RG was significantly higher than it was in the CG (P<0.05) (Table 4).

Comparison of the 6MWT and CAT scores

In this study, 6MWT and CAT were used to evaluate the patients’ conditions. The results revealed that there were no significant differences in the 6MWT and CAT scores in the two groups before the therapy (P>0.05). After the therapy, the 6MWT scores in both groups were higher than they were before the therapy (P<0.001), and the CAT scores were lower than

Table 1. Scoring criteria for the clinical symptoms and signs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Scoring criteria</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughing</td>
<td>No coughing</td>
<td></td>
<td>Occasional coughing</td>
<td>Frequent coughing</td>
<td>Severe coughing</td>
</tr>
<tr>
<td>Expectoration</td>
<td>No phlegm</td>
<td></td>
<td>The amount of expectoration was less</td>
<td>The amount of expectoration ranged</td>
<td>The amount of expectoration was more</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>than 15 ml</td>
<td>from 15 ml to 50 ml</td>
<td>than 50 ml</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>The patient did not</td>
<td></td>
<td>The patient had dyspnea</td>
<td>The patient had dyspnea and it stopped</td>
<td>The patient was unable to walk long</td>
</tr>
<tr>
<td></td>
<td>have dyspnea until he</td>
<td></td>
<td>until he continued to walk quickly</td>
<td>when he walked quickly on flat ground</td>
<td>distances and had severe dyspnea</td>
</tr>
<tr>
<td></td>
<td>continued to exercise</td>
<td></td>
<td>on flat ground</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>No rales</td>
<td></td>
<td>Occasional rales</td>
<td>Scattered rales</td>
<td>Full-lung rales</td>
</tr>
</tbody>
</table>

Table 2. Evaluation criteria of efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Evaluation criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markedly effective</td>
<td>The clinical symptoms improved significantly and disappeared completely. The sputum was easy to cough up. The respiratory function improved significantly.</td>
</tr>
<tr>
<td>Effective</td>
<td>The clinical symptoms were improved. The sputum was easy to cough up. The respiratory function was improved.</td>
</tr>
<tr>
<td>Ineffective</td>
<td>The symptoms and respiratory function were not improved.</td>
</tr>
</tbody>
</table>
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They were before the therapy (P<0.001), The 6MWT scores in the RG were higher than they were in the CG (P<0.001), and the CAT scores were significantly lower than they were in the CG (P<0.001) (Table 5).

Changes in the serum inflammatory cytokine levels

By measuring the serum inflammatory cytokine levels in both groups, it was found that there was no significant difference in the IL-6, IL-8, and TNF-α levels between the CG and RG before the therapy (P>0.05). After the therapy, the IL-6, IL-8, and TNF-α levels in both groups were lower than they were before the therapy (P<0.001), and the IL-6, IL-8, and TNF-α levels in the RG were significantly lower than they were in the CG (P<0.001) (Figures 2, 3).

The improvement of lung function in both groups

There were no significant differences in the PEF, FEV1, or FVC levels in the two groups before the therapy (P>0.05). After the therapy,
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Table 4. The clinical efficacy in both groups

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG (n=69)</td>
<td>21 (30.43)</td>
<td>29 (42.03)</td>
<td>19 (27.54)</td>
<td>50 (72.46)</td>
</tr>
<tr>
<td>RG (n=73)</td>
<td>34 (46.58)</td>
<td>32 (43.84)</td>
<td>7 (9.59)</td>
<td>66 (90.41)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 7.639 \]

\[ P = 0.006 \]

Table 5. Changes in the 6MWT and CAT scores

<table>
<thead>
<tr>
<th>Grouping</th>
<th>6MWT Before treatment</th>
<th>6MWT After treatment</th>
<th>CAT Before treatment</th>
<th>CAT After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG (n=69)</td>
<td>237.47±48.25</td>
<td>318.65±45.62*</td>
<td>26.27±2.75</td>
<td>16.14±2.23</td>
</tr>
<tr>
<td>RG (n=73)</td>
<td>248.75±51.23</td>
<td>362.16±44.86*</td>
<td>25.92±2.87</td>
<td>12.37±2.51</td>
</tr>
</tbody>
</table>

\[ t = 1.349 \]

\[ P = 0.180 \]

\[ * \text{indicates } P < 0.05. \]

Discussion

The pathogenesis of COPD is complex. Although progress has been made in the treatment and prevention of disease, there has been little progress in improving patient prognosis, confirming that COPD is still a major health care problem at present [19]. If a patient is not treated effectively, the patient will progress to an acute exacerbation of COPD. Respiratory viruses and bacteria can infect the lower respiratory tract, aggravate respiratory inflammation, exacerbate the patient’s symptoms, decrease lung function, seriously affect the quality of life, and increase medical expenditures [20]. Therefore, it is very important to seek effective treatment to prevent the progression of the disease.

Bronchodilators are the key to the symptomatic treatment of COPD [21]. However, bronchodilators are relatively expensive and may increase the incidence of adverse complications, especially in elderly patients [22, 23]. ABH combined with antibacterial drugs is an effective way to prevent drug-resistant bacterial infections, and the combination can decrease drug dose demand, reduce drug toxicity, and prevent or delay the emergence of drug resistance [24]. Based on the above research, it is considered that ABH is a more appropriate choice for adjuvant symptomatic treatment, so we will verify its therapeutic effect. In this study, the clinical symptoms and sign scores were compared between the two groups. The results indicated that the sign scores in both groups were decreased after the therapy compared with the pretreatment scores, indicating that the treatment in both groups effectively relieved the patients’ clinical symptoms. However, the patients’ scores in the RG were significantly lower than they were in the CG, indicating that ABH adjuvant therapy has a better effect at relieving the clinical symptoms. Then, the therapeutical effective rates were analyzed in both groups, and the results indicated that ABH combined treatment is more effective for elderly patients with COPD. ABH, a drug used for dissolving bronchial sputum, is widely used in respiratory diseases [25]. Studies have revealed that ABH has an excellent clinical effectiveness at preventing and treating RDS. It can improve patients’ symptoms such as dyspnea, and it can effectively prevent neonatal death in prenatal applications [26, 27], a conclusion similar to the results of our research.
We believe that ABH can relieve dyspnea by diluting sputum and alleviating bronchial blockages, and it helps to relax the smooth muscle of the respiratory tract and achieve good spasmolysis and antiasthmatic effects. 6MWT and CAT are commonly-used clinical tools for evaluating the athletic abilities and conditions of patients with COPD [28, 29]. After the therapy, it was found that the 6MWT scores of the patients in the RG were significantly higher than they were in the CG, while the CAT scores were significantly lower than they were in the CG, indicating that compared with the conventional treatment, ABH adjuvant therapy can significantly improve the athletic abilities of patients and ameliorate their conditions.

COPD mainly causes respiratory obstructions and is related to chronic inflammation of the respiratory tract. The main symptoms are lung rales, fever, and cough [30, 31]. Ventilation obstructions are caused by a thickening of the respiratory membrane and the obstruction of the lower respiratory tract due to lung inflammation. In this study, the serum inflammatory cytokine levels in both groups were tested after the therapy. The results revealed that the serum inflammatory cytokine levels in the RG were significantly lower than they were in the CG, which indicated that ABH can significantly improve patients’ inflammatory responses. Biofilm is a key factor in the development of respiratory tract infections, and microorganisms are resistant to many drugs. Ambroxol can inhibit the activity of neutrophils and play an anti-inflammatory role, and it interferes with the activity of the ion channels and transporters in the respiratory epithelia to improve the mucociliary clearance and ameliorate biofilm-dependent respiratory tract infections [32]. COPD is caused by the long-term inhalation of toxic particles and gases, which leads to persistent congenital and adaptive immune responses in the lungs, and it participates in abnormal tissue repair and remodeling, leading to chronic inflammation, an excessive production of mucus in the respiratory tract, and the disruption of gas exchange [33]. In this study, the patients’ cellular immune function indexes were tested in both groups. The findings revealed that the immune function of the patients in the RG was significantly ameliorated after the therapy, indicating that ABH combined with conventional treatment such as antibiotics can effectively improve patients’ immune function. Inflammation plays a vital role in the control of pathogens and the formation of the subsequent adaptive immunology responses. The combination of an inflammatory response regulated by memory and effector
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A  Before therapy

CD3  74.38%

CD3  86.12%

After treatment

CD3  66.65%

CD3  68.74%

B  Before therapy

CD4  44.52%

CD4  47.25%

After treatment

CD4  43.72%

CD4  44.83%
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Figure 3. Flow cytometry.
T cell function can better control infections [34, 35]. Therefore, we believe that ABH combined with antibacterial drugs has a better anti-inflammatory effect, thus improving the immune function. The long-term use of ambroxol, a bronchial expectorant, can prevent the acute exacerbation of COPD [36]. Our study has revealed that the short-term use of ABH is effective. At the completion of the study, the incidence of adverse effects was analyzed in both groups. The findings revealed that there was no significant difference in the incidence of adverse effects between the two groups, indicating that the application of ABH in elderly patients with COPD is safe and worthy of clinical promotion.

This study has revealed that ABH has a high clinical effectiveness in elderly patients with COPD, but there are still some shortcomings in

Table 6. Changes in the pulmonary function indexes

<table>
<thead>
<tr>
<th></th>
<th>PEF (L/S)</th>
<th>FEV1 (L)</th>
<th>FVC (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td>1.77±0.41</td>
<td>1.98±0.44*</td>
<td>0.87±0.29</td>
<td>1.65±0.33*</td>
</tr>
<tr>
<td>1.75±0.45</td>
<td>2.51±0.47*</td>
<td>0.85±0.31</td>
<td>1.91±0.38*</td>
</tr>
<tr>
<td>0.276</td>
<td>6.927</td>
<td>0.397</td>
<td>4.343</td>
</tr>
<tr>
<td>0.783</td>
<td>&lt;0.001</td>
<td>0.692</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: *indicates P < 0.05.

Figure 4. Changes in the immune function indexes. A. Before the therapy, there was no significant difference in the serum CD3+ levels between the two groups. After the therapy, the CD3+ levels in both groups were higher than they were before the therapy, and the CD3+ levels in the RG were significantly higher than they were in the CG. B. Before the therapy, there was no significant difference in the serum CD4+ levels between the two groups. After the therapy, the CD4+ levels in the RG were higher than they were before the therapy, and the CD4+ levels in the RG were significantly higher than they were in the CG. C. Before the therapy, there was no significant difference in the serum CD8+ levels between the two groups. After the therapy, the CD8+ levels in both groups were lower than they were before the therapy, and the CD8+ levels in the RG were significantly lower than they were in the CG. **P<0.01, ***P<0.001.

Table 7. Comparison of the incidences of adverse reactions

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Gastrointestinal reaction</th>
<th>Dizziness</th>
<th>Nausea and vomiting</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG (n=69)</td>
<td>2 (2.90)</td>
<td>3 (4.35)</td>
<td>1 (1.45)</td>
<td>6 (8.70)</td>
</tr>
<tr>
<td>RG (n=73)</td>
<td>4 (5.48)</td>
<td>3 (4.11)</td>
<td>2 (2.74)</td>
<td>9 (12.33)</td>
</tr>
<tr>
<td>χ²</td>
<td>0.496</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.481</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
this research. We did not evaluate the patients' treatment compliance. Compliance is affected by many factors, and it may affect the therapeutic effect [37]. Therefore, in future research, we will address this shortcoming.

In conclusion, this study found that ABH can effectively relieve the clinical symptoms, reduce the inflammation, and improve the lung function of elderly patients with COPD, and it has a significant clinical effectiveness and is very safe, so it is worthy of promotion.

Disclosure of conflict of interest

None.

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