Application of bronchoalveolar lavage combined with ambroxol in elderly patients with severe pneumonia and its effect on serum sTREM-1 level

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Received June 12, 2020; Accepted August 4, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: This study aimed to explore the treatment efficacy of bronchoalveolar lavage (BAL) combined with ambroxol for senile severe pneumonia (SP) and its effect on serum levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1). Methods: A total of 168 patients with SP treated in our hospital from May 2016 to December 2018 were randomized to receive routine treatment and BAL (76 cases, the control group, CG) or to receive routine treatment and BAL combined with ambroxol (92 cases, the research group, RG). The two groups were compared in terms of clinical efficacy, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, recovery of clinical symptoms, markers for lung function, blood gas markers, and serum sTREM-1 level. Results: The improvement in clinical indicators was greater in the RG than in the CG. The improvement in blood gas markers and markers for lung function were greater in the RG than in the CG. The APACHE II score after treatment was markedly lower in the RG than in the CG. The concentration of sTREM-1 after treatment was markedly lower in the RG than in the CG. There was a positive correlation between the concentration of sTREM-1 and the APACHE II score after treatment in the RG. The overall response rate was markedly higher in the RG than in the CG. Conclusion: BAL combined with ambroxol is effective in treating senile SP and promotes the recovery and improvement of lung function. sTREM-1 is a potential reference index to evaluate the improvement of the patient’s condition.

Keywords: Bronchoalveolar lavage, ambroxol, pneumonia, sTREM-1

Introduction

Pneumonia attacks 450 million individuals worldwide and causes nearly 4 million deaths each year. As a common reason for admission to the intensive care unit, severe pneumonia (SP), if not properly treated, may rapidly develop into septic shock, respiratory failure, or cause death within a few days [1-3]. SP is the main factor behind the morbidity and mortality in the elderly, what’s worse, the number of elderly patients affected by SP is increasing according to epidemiological trends [4, 5]. Existing treatments for SP mainly rely on antibiotics [6, 7]. Development of the social economy in recent years leads to an increased incidence of common basic diseases and accompanying decreased sensitivity to antibiotics in patients [8]. Therefore, it is essential to find practical and safe treatment therapies for SP with favorable efficacy.

Bronchoalveolar lavage (BAL), is minimally invasive and safe, and it can target the lesion under the view of the fiberoptic bronchoscope to clear the respiratory tract secretions, effectively relieve airway obstruction, and restore airway ventilation [9, 10]. BAL can also selectively drain out viscous secretions and sputum to ensure airway patency [11]. However, routine antibiotics used in patients receiving BAL can easily cause drug resistance, which impairs treatment efficacy. Here we used BAL combined with ambroxol to treat SP patients [12]. Ambroxol is a metabolite of bromhexine widely used clinically for airway diseases or phlegm-dispelling [13]. It can promote bronchial epithelial repair and accelerate the trans-
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Port of mucosal cilia [14]. Ambroxol has extensive pharmacological anti-inflammatory properties \textit{in vivo} and \textit{in vitro}, such as inhibiting or clearing oxidative stress or nitrosative stress and promoting local defense molecules associated with respiratory virus replication [15]. In the study by Yang Z et al., ambroxol effectively improved the lung function markers in newborns with pneumonia, reduced serum levels of inflammatory mediators, inhibited cell apoptosis, activated the NF-κB pathway, and enhanced lung function [16]. sTREM-1 is a unique form of TREM-1 clinically recognized as a biomarker for infectious diseases, which can be tested directly in human body fluids to diagnose infectious diseases such as lung infections, pleural effusions, and viral infections and predict prognosis [17, 18].

This study investigated the application value of BAL combined with ambroxol in the treatment of senile SP, tested serum sTREM-1 concentrations before and after treatment, and assessed the efficacy and prognosis of all patients, aiming to provide a better reference for the treatment of SP in elderly patients.

\textbf{Materials and methods}

\textbf{Basic information}

A total of 168 patients with SP treated in our hospital from May 2016 to December 2018 were randomized to receive routine treatment and BAL (76 cases, the control group, CG) or to receive routine treatment and BAL combined with ambroxol (92 cases, the research group, RG). Inclusion criteria: Patients diagnosed with SP [19]; patients with stable vital signs; patients capable of independent thinking; patients with complete clinical data; patients with an expected survival of \(\geq 1\) year. This study was approved by the Ethics Committee of our hospital. All patients and their family members signed the written informed consent. Exclusion criteria: Patients lost to the follow-up; patients with liver, kidney, or hematopoietic dysfunction; patients with end-stage diseases, multiple organ dysfunction, or in shock; patients allergic to drugs used in this study; patients with severe pulmonary hypertension, impaired central nervous system, history of mental illness, or family history of SP; patients who withdrew from the study midway; patients who left the hospital without permission.

\textbf{Treatment methods}

Patients in the CG were given routine treatment first (conventional anti-infection treatment, nutritional support, postural drainage, and symptomatic treatment). Then patients were treated with BAL. We gave 5 mg of midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., Jiangsu, China, China Food and Drug Administration Approval No. H20031037) for sedation, connected the fiberoptic bronchoscope to a negative pressure aspirator, and gave patients an inhalation of high-concentration oxygen for about 5 minutes under ECG monitoring. When the patient’s blood oxygen saturation reached 95% or greater, we inserted the fiberoptic bronchoscope through the mouth, nose, or artificial airway, examined the patient’s total trachea, trachea segments, and subsegmental bronchi quickly, and sucked out the secretions. Then we gave 15-20 mL of 0.9 sodium chloride solution (Shanghai Yuanye Bio-Technology Co., Ltd., Shanghai, China, item number: R21092) to irrigate the lesion and sucked the solution 1 minute afterwards. The negative pressure was controlled \(\leq 100\) mmHg (1 mmHg = 0.133 kPa) during the wash. If the blood oxygen saturation was less than 85%, we stopped the operation immediately and took out the fiberoptic bronchoscope, followed by an oxygen supply. The wash continued when the patient’s blood oxygen saturation reached 95% or greater again. Each lung segment of the lesion was washed repeatedly until the lavage fluid was clear (the number of lavages \(\geq 3\) times, the total lavage volume \(\leq 100\) ml/time).

Patients in the RG were given ambroxol based on the treatment regimen designed for patients in the CG. We mixed 250 mL of sterile saline with 120 mL of ambroxol (SHANGHAI ZZBIO Co., Ltd., Shanghai, China, item number: IR43676) to wash the lesion. The total amount of lavage fluid was 100-200 mL each time, 2-3 times per week. The treatment for both groups lasted for 1 week.

\textbf{Outcome measures}

\textbf{Clinical symptoms:} We recorded the mechanical ventilation time, time of recovery from atelectasis, time of recovery from abnormal temperature, time of recovery from respiratory failure, and hospitalization time after treatment intervention.
Blood gas analysis: At 24 hours before and after treatment, we collected 5 mL arterial blood from each patient, injected it into the heparin cap, and stored the blood sample in a cooling package below 8°C. Then we measured the partial pressure of carbon dioxide (PaCO\(_2\)), partial pressure of oxygen artery (PaO\(_2\)), and pH value in the blood samples on a blood gas analyzer (Shanghai Yuyan Instruments Co., Ltd., Shanghai, China, item number: 57984).

Lung function markers: We measured the forced vital capacity (FVC), forced expiratory volume (FEV) in the first second (FEV\(_1\)), FEV\(_1\)/FVC, maximum mid-expiratory flow (MMF), and the peak expiratory flow (PEF) of patients before and after treatment on a lung function test instrument (Beijing Zeao Medical Technology Co., Ltd., Beijing, China, item number: z00502).

Acute Physiology and Chronic Health Evaluation II (APACHE II) score [20]: The score was assessed based on three indicators, ranging from 0 to 71 points. A higher score indicates a more serious condition.

Concentration of soluble myeloid cell trigger receptor-1 (sTREM-1): We took 5 mL venous blood from the elbow of patients 24 hours before and after treatment and centrifugated the blood sample at 1500 \( \times \) g for 10 minutes at 4°C. Then the sample was stored in a -70°C freezer. Then we detected the concentration of sTREM-1 using the enzyme-linked immunosorbent assay (ELISA) [21] following...
the instructions of the sTREM-1 kit (Shanghai Hengdu Biotechnology Co., Ltd., Shanghai, China, item number: HD38923).

**Efficacy:** We assessed the efficacy for all patients after treatment, which was divided into three levels: marked response, moderate response, and no response. A marked response referred to normal clinical symptoms and arterial blood gas markers and regular chest radiograph results. A moderate response referred to mitigated clinical symptoms, improved arterial blood gas markers, and alleviated inflammation according to the chest radiograph. No response referred to the absence of notable changes in clinical symptoms and blood gas markers or a worsened condition, and severe inflammation according to the chest radiograph. Overall response rate = (number of cases with marked responses + moderate responses)/total case number × 100%.

**Statistical analysis**

Statistical analysis was performed by SPSS 21.0 (EASYBIO, Beijing, China). The count data were represented by the number of cases/percentage [n (%)] and compared between the two groups using the chi-square test. The measurement data were represented by the mean ± standard deviation (mean ± SD), which were compared between the two groups using the independent sample t-test and compared within the group using the paired t-test. Pearson correlation coefficient was used for correlation analysis. Data visualization was performed on GraphPad Prism 6 software. The difference was statistically significant when P < 0.05.

**Results**

**Basic information**

The comparison between the two groups showed no significant difference in sex, age, BMI, time of disease onset, place of residence, ethnicity, educational background, smoking history, drinking history, hypertension history, diabetes history, systolic blood pressure, and diastolic blood pressure (P > 0.05). More details are shown in Table 1.

**Comparison of improvements in clinical symptoms**

After treatment, the mechanical ventilation time, time of recovery from atelectasis, time of recovery from abnormal temperature, time of recovery from respiratory failure, and hospitalization time were markedly shorter in the RG than in the CG (P < 0.05). More details are shown in Table 2.

**Comparison of blood gas markers**

The differences between the two groups in PaCO\(_2\), PaO\(_2\), and pH levels before treatment were not significant (P > 0.05). After treatment, blood gas markers were improved in both groups (P < 0.05), with markedly lower PaCO\(_2\) level and markedly higher PaO\(_2\) and pH levels.
Table 4. Markers for lung function in the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Case number</th>
<th>FVC (L)</th>
<th>FEV₁ (L)</th>
<th>FEV₁/FVC (%)</th>
<th>MMF (L)</th>
<th>PEF (L/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>RG</td>
<td>92</td>
<td>2.03 ± 0.14</td>
<td>2.57 ± 0.41</td>
<td>1.31 ± 0.21</td>
<td>1.84 ± 0.26</td>
<td>59.86 ± 4.61</td>
</tr>
<tr>
<td>CG</td>
<td>76</td>
<td>2.02 ± 0.11</td>
<td>2.31 ± 0.37</td>
<td>1.27 ± 0.24</td>
<td>1.53 ± 0.21</td>
<td>59.34 ± 4.35</td>
</tr>
<tr>
<td>t</td>
<td>-</td>
<td>0.506</td>
<td>4.274</td>
<td>1.152</td>
<td>8.378</td>
<td>0.746</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Comparison of markers for lung function

The two groups were not notably different in markers for lung function before treatment (P > 0.05). After treatment, markers for lung function were markedly improved in both groups (P < 0.05), with markedly higher FVC, FEV₁, FEV₁/FVC, MMF, and PEF levels in the RG than in the CG (P < 0.05). More details are shown in Table 4.

Comparison of APACHE II score

The two groups were not notably different in the APACHE II score before treatment (P > 0.05). After treatment, the APACHE II score was markedly lower in the RG than in the CG (P < 0.05). More details are shown in Figure 1.

Comparison of sTREM-1 concentration

The two groups were not notably different in the sTREM-1 concentration before treatment (P > 0.05). After treatment, the sTREM-1 concentration was markedly lower in the RG than in the CG (P < 0.05). More details are shown in Figure 2.

Correlation between serum sTREM-1 concentration and APACHE II score after treatment in the RG

The results of the Pearson correlation coefficient revealed a positive correlation between the serum sTREM-1 concentration and the APACHE II score after treatment in the RG (r = 0.690, P < 0.05). More details are shown in Figure 3.

Comparison of treatment efficacy

The overall response rate was markedly higher in the RG than in the CG (91.3% vs. 80.26%, P < 0.05). More details are shown in Table 5.
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Table 5. Treatment responses in the two groups [n (%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>Case number</th>
<th>Marked response</th>
<th>Moderate response</th>
<th>No response</th>
<th>Overall response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG</td>
<td>92</td>
<td>58 (63.04)</td>
<td>26 (28.26)</td>
<td>8 (8.70)</td>
<td>84 (91.30)</td>
</tr>
<tr>
<td>CG</td>
<td>76</td>
<td>22 (28.95)</td>
<td>39 (51.32)</td>
<td>15 (19.74)</td>
<td>61 (80.26)</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.294</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.038</td>
</tr>
</tbody>
</table>

Discussion

Pneumonia is a major public concern especially for the elderly, with high morbidity and mortality among senior people [22]. Pneumonia in the elderly, has quick onset and a poor prognosis, it can easily develop into SP, which causes a mortality rate of 24% mainly due to impaired respiratory function [23]. The airway secretions increase and get sticky in patients with pneumonia, eventually causing a vicious circle [24]. Damaged airway ventilation and aggravated local airway inflammation resulting from airway obstruction often impairs the effect of antibiotics [25]. Therefore, it is quite crucial to effectively clean up the respiratory secretions in patients and relieve airway obstruction.

Here we used BAL combined with ambroxol to treat elderly patients with SP and found a better prognosis in patients. The study by Wang LP and his team [26] suggests that early alveolar lavage with flexible bronchoscopy can relieve clinical symptoms of children with respiratory diseases and improve the prognosis. The study by Chen F et al. [27] revealed that ambroxol hydrochloride alleviated alveolitis and pulmonary fibrosis in rat models of pulmonary fibrosis, as well as supported anti-infection treatment in the early stages of fibrosis. In this study, the improvements in clinical indicators of patients were markedly greater in the RG than in the CG, which shows that BAL combined with ambroxol can effectively dissolve the viscous substances in the airway, decrease airway obstruction, increase inhaled oxygen flow, and improve the patient's lung function.

The APACHE II score is a prognostic indicator for patients in the intensive care unit [29]. A previous study revealed that the increase in the APACHE II score leads to increased incidence of delirium in elderly patients with SP receiving invasive mechanical ventilation, suggesting that the APACHE II score is important in evaluating the incidence of delirium in elderly patients with SP [30]. In the present study, the APACHE II score after treatment was markedly lower in the RG than in the CG, indicating that BAL combined with ambroxol can effectively decrease the severity of the patient’s condition. sTREM-1 is a pro-inflammation mediator that is involved in the inflammatory process of SP and works as a marker for the diagnosis and severity assessment of patients with SP [31, 32]. In the present study, the sTREM-1 concentration after treatment was markedly lower in the RG than in the CG, indicating that BAL combined with ambroxol can reduce inflammation and improve the patient’s condition and prognosis. Here we detected a decrease in both the APACHE II score and the sTREM-1 concentration during the treatment and the decrease in the two groups was significantly and positively correlated, indicating that patients undergoing BAL combined with ambroxol have a good prognosis. After treatment, the overall response rate was markedly higher in the RG than in the CG, indicating that BAL combined with ambroxol is highly effective in treating senile SP and relieving conditions.

This study confirmed that BAL combined with ambroxol is a feasible treatment plan for elderly patients with SP, but it is subject to some deficiencies. For example, we did not evaluate the quality of life of patients and analyze the diagnostic value of sTREM-1 for SP, nor did we
explore risk factors that affect the efficacy of treatment for elderly patients with SP. We will address these deficiencies in future research. In summary, BAL combined with ambroxol is markedly effective in the treatment of SP in elderly patients and promotes the recovery and improvement of lung function. sTREM-1 is a potential reference index to evaluate the improvement of patients conditions.

Disclosure of conflict of interest

None.

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