Effect of azithromycin, terbutaline combined with montelukast on airway function and gradient of infection in cough variant asthma children with infection

Xin-Xin Pei

Infectious Disease Department, Xuzhou Children’s Hospital of Jiangsu Province, Xuzhou City, Jiangsu Province, 221000

ARTICLE INFO

Article history:
Received 9 Aug 2016
Received in revised form 20 Aug 2016
Accepted 12 Aug 2016
Available online 24 Aug 2016

Keywords:
Cough variant asthma
Montelukast
Terbutaline
Airway function

ABSTRACT

Objective: To analyze the effect of azithromycin, terbutaline combined with montelukast on airway function and gradient of infection in cough variant asthma children with infection.

Methods: A total of 116 cases of cough variant asthma children with infection were included in the study and randomly divided into observation group and control group (n=58), control group received azithromycin treatment, observation group received azithromycin, terbutaline combined with montelukast treatment, and then differences in basic lung function and small airway function, asthma attack and airway remodeling-related indicators, infection-related indicators, etc. were compared between two groups after treatment.

Results: Basic lung function indexes FEV1 and FVC of observation group after treatment were significantly higher than those of control group, and small airway function indexes MMEF, FEF50% and FEF75% were significantly lower than those of control group; serum ECP, IgE, IL-5, MMP-2, MMP-9, TIMP-1, PET, CRP and IL-4 levels of observation group after treatment were lower than those of control group while IFN-γ and hBD-1 levels were higher than those of control group.

Conclusion: Azithromycin, terbutaline combined with montelukast can improve airway function and infection status and promote disease rehabilitation in cough variant asthma children with infection.

1. Introduction

Cough variant asthma (CVA) belongs to the special type of bronchial asthma with the major pathological manifestation of respiratory inflammatory stimuli. Study has shown that the proportion of CVA patients with mycoplasma infection is higher, and it is believed that mycoplasma infection is an important reason leading to occurrence and development of CVA[1]. The treatment difficulty is higher for CVA patients with mycoplasma infection, combined use of other drugs based on conventional asthma-relieving and spasmolysis treatment is needed to enhance curative effect and reduce the risk of CVA progression to severe asthma. Azithromycin is the most common antibiotic in the clinical treatment of CVA patients with infections, and can alleviate symptoms of cough in CVA patients[2,3]. Terbutaline is a highly selective β2 receptor agonist that can relax bronchial smooth muscle and inhibit mastocytes from releasing inflammatory and allergic mediators; montelukast is CysLT1 receptor antagonist that can inhibit leukotriene receptor activity and reduce airway hyperresponsiveness in CVA patients[4]. The high-risk groups of CVA are young children, cough variant asthma children with mycoplasma infection treated in our hospital from December 2013 to December 2015 were selected as the research subjects of the study, and azithromycin, terbutaline and montelukast are used together for the treatment, hereby reported as follows.

2. Research subjects and methods

2.1. Research subjects
A total of 116 cases of cough variant asthma children with infection were included in the study, inclusion criteria: 1) in accordance with the diagnostic standard for cough variant asthma established by WHO; 2) positive in throat swab detection of mycoplasma; 3) families of children signed informed consent. Exclusion criteria: (1) with foreign body in airway; 2) with basic sinusitis, bronchitis, tuberculosis, etc.; 3) associated with congenital cardiopulmonary diseases; 4) associated with severe liver and kidney function damage. Above children were randomly divided into observation group and control group (n=58), observation group included 31 male cases and 27 female cases, they were 2-7 years old, the average age was (4.17±0.53) years, the course of cough variant asthma was 3-14 months and the average course was (6.83±0.75) months; control group included 30 male cases and 28 female cases, they were 1-8 years old, the average age was (4.36±0.51) years, the course of cough variant asthma was 2-13 months and the average course was (6.95±0.72) months. Two groups were not statistically different in gender, age and course of asthma (P>0.05), and they were comparable.

2.2. Treatment methods

Both groups received conventional treatment such as phlegm-eliminating and cough-stopping, asthma-relieving and anti-infection, control group received azithromycin granules, 10 mg/kg (total daily dose not more than 0.5 g), administered at draught on the first day and 5 mg/(kg•d) (maximum daily dose not more than 0.25 g), administered at draught on the 2-5 d. Based on the treatment of control group, observation group received terbutaline and montelukast treatment, specifically as follows: aerosol inhalation of Terbutaline Sulphate Solution for Nebulization, aerosol inhalation of 2.5 mg (1 mL) solution for those with body mass <20 kg and the total daily number 4 times; aerosol inhalation of 5 mg (2 mL) solution for those with body mass 20 kg and the total daily number 4 times; montelukast chewable tablets 5 mg/time, 1 time/d. 3 month was 1 treatment course for the above treatment, and during the therapy, the airway function, infection severity and other basic conditions were followed up.

2.3. Observation indexes

2.3.1. Basic lung function and small airway function

1 month after treatment, MS-PFT pulmonary function test apparatus was used to detect the basic lung function and small airway function of two groups, basic lung function: forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Small airway function: maximum mid-expiratory flow (MMEF), forced expiratory flow at 50% remaining forced vital capacity (FEF50%) and forced expiratory flow at 75% remaining forced vital capacity (FEF75%).

2.3.2. Asthma attack and airway remodeling–related indicators

1 month after treatment, 2ml of fasting peripheral venous blood was collected from two groups, let stand at room temperature for 60 min and then centrifuged at low speed (3 000 r/min), and supernatant was collected for subsequent use. Enzyme-linked immunofluorescence was used to quantitatively determine serum asthma-related indexes, including eosinophil cationic protein (ECP), IgE and interleukin-5 (IL-5). Double antibody sandwich enzyme-linked immunosorbent assay was used to determine serum airway remodeling-related parameters, including matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1).

2.3.3. Infection–related indicators

1 month after treatment, 2 mL of fasting peripheral venous blood was collected from two groups, and enzyme-linked immunosorbent assay was used to determine serum infection-related indexes procalcitonin (PET), C-reactive protein (CRP), interleukin-4 (IL-4), interferon-γ (IFN-γ) and human β-defensin-1 (hBD-1) levels.

2.4. Statistical methods

SPSS 23.0 software was used to input and analyze data, measurement data comparison between groups was by t test, count data was by chi-square test and P<0.05 indicated statistical significance in differences.

3. Results

3.1. X ray examination

Imaging examination is an important way to determine the respiratory system disease, cough variant asthma children with infection may be accompanied by abnormal X-ray image performance, and it is the most common imaging method to

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>FEV1</th>
<th>FVC</th>
<th>MMEF</th>
<th>FEF50%</th>
<th>FEF75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>58</td>
<td>1.92±0.22</td>
<td>2.32±0.27</td>
<td>1.45±0.22</td>
<td>1.55±0.21</td>
<td>1.26±0.15</td>
</tr>
<tr>
<td>Control</td>
<td>58</td>
<td>1.52±0.18</td>
<td>2.14±0.25</td>
<td>2.04±0.28</td>
<td>2.33±0.27</td>
<td>1.91±0.17</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>7.394</td>
<td>8.192</td>
<td>5.372</td>
<td>7.394</td>
<td>8.172</td>
</tr>
<tr>
<td>P</td>
<td></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>
judge the disease severity and treatment effect. In the study, X-ray examination was conducted before and after treatment, X-ray images of two groups before treatment showed enlargement of the trachea and pulmonary patchy exudation, the above X-ray performance was relieved in different extent after treatment, the airway enlargement shadow of observation group almost disappeared, lung tissue texture was even, and there was no patchy shadow.

3.2. Basic lung function and small airway function

Analysis of basic lung function indexes FEV1 and FVC of two groups after different treatment was as follows: basic lung function indexes FEV1 and FVC of observation group after treatment were significantly higher than those of control group, and differences were statistically significant ($P<0.05$); analysis of small airway function indexes MMEF, FEF$_{50}$% and FEF$_{75}$% of two groups after different treatment was as follows: small airway function indexes MMEF, FEF$_{50}$% and FEF$_{75}$% of observation group after treatment were significantly lower than those of control group, and differences were statistically significant ($P<0.05$), shown in Table 1.

3.3. Asthma attack and airway remodeling–related indicators

There are airway hyperresponsiveness and airway remodeling in cough variant asthma children with infection, and analysis of asthma attack indexes ECP, IgE and IL-5 of two groups was as follows: serum ECP, IgE and IL-5 levels of observation group after treatment were lower than those of control group; analysis of airway remodeling indexes MMP-2, MMP-9 and TIMP-1 of two groups was as follows: serum MMP-2, MMP-9 and TIMP-1 levels were higher than those of control group, and differences were statistically significant ($P<0.05$), shown in Table 2.

3.4. Infection–related indicators

Cough variant asthma with infection can worsen asthma conditions, and the levels of infection-related indexes are closely related to the severity of asthma. In the study, analysis of serum infection-related indexes PET, CRP, IL-4, IFN-γ and hBD-1 of two groups was as follows: serum PET, CRP and IL-4 levels of observation group after treatment were lower than those of control group, IFN-γ and hBD-1 levels were higher than those of control group, and differences in serum levels between two groups were statistically significant ($P<0.05$), shown in Table 3.

4. Discussion

Cough variant asthma (CVA) is a special type of asthma with the main performance of respiratory inflammatory stimulation, and studies have shown that mycoplasma pneumoniae infection is correlated with cough variant asthma, and many CVA patients are accompanied by mycoplasma infection, which can induce asthma attack and aggravate the illness. Young children are the main population with CVA, and active treatment is needed for CVA patients with infection to avoid that disease progresses to conventional asthma and endangers children’s safety[5,6]. For CVA children with infection, in addition to the conventional treatment such as antianaphylaxis and spasmolysis, azithromycin was mostly adopted for clinical anti-infection treatment. Through phagocyte transmission mechanism, azithromycin transfers it to inflammatory parts of the body, reaches local high concentration, exerts strong antibacterial effect, and can relieve the symptoms of CVA cough caused by mycoplasma infection[7]. Current clinical studies have found that the curative effect of azithromycin alone is limited for anti-inflammatory treatment of children with CVA and some children are not sensitive to azithromycin, which restricts its clinical application. Multi-drug combination therapy is the latest treatment principle for CVA children with infection, azithromycin, terbutaline combined with montelukast are used to treat CVA children with mycoplasma infection in the study, terbutaline is a highly selective β2 receptor agonist that has potently exciting effect on β2 receptor, can relax bronchial smooth muscle, inhibit mastocytes from releasing inflammatory and allergic mediators, enhance airway cilia movement and reduce airway mucosa edema, and plays a positive role in alleviating bronchospasm and airway stenosis[8,9].

Table 2.
Comparison of asthma attack and airway remodeling–related indicator values between two groups after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>ECP (ng/L)</th>
<th>IgE (ku/L)</th>
<th>IL-5 (pg/mL)</th>
<th>MMP-2 (pg/L)</th>
<th>MMP-9 (ng/L)</th>
<th>TIMP-1 (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>58</td>
<td>8.43±0.92</td>
<td>85.35±11.11</td>
<td>1.76±0.23</td>
<td>1324.73±178.95</td>
<td>241.26±29.75</td>
<td>201.36±25.47</td>
</tr>
<tr>
<td>Control</td>
<td>58</td>
<td>11.76±1.84</td>
<td>121.46±17.83</td>
<td>2.84±0.35</td>
<td>1623.81±201.32</td>
<td>285.43±31.27</td>
<td>246.38±30.79</td>
</tr>
<tr>
<td>P</td>
<td></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 3.
Comparison of serum infection-related indicator values between two groups after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>PET (µg/L)</th>
<th>CRP (mg/L)</th>
<th>IL-4 (pg/mL)</th>
<th>IFN-γ (mg/mL)</th>
<th>hBD-1 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>58</td>
<td>1.27±0.18</td>
<td>7.52±0.83</td>
<td>32.65±4.12</td>
<td>45.72±5.61</td>
<td>14.73±2.04</td>
</tr>
<tr>
<td>Control</td>
<td>58</td>
<td>7.31±0.85</td>
<td>19.61±2.43</td>
<td>48.41±5.76</td>
<td>37.23±4.09</td>
<td>10.32±1.63</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>7.331</td>
<td>9.832</td>
<td>8.463</td>
<td>9.364</td>
<td>7.283</td>
</tr>
<tr>
<td>P</td>
<td></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>
Montelukast is the strongest specific CysLT1 receptor antagonist that can effectively inhibit the leukotriene receptor activity and the effect of peptide growth factor on promoting acidophilic granulocyte maturation, and reduce the patients’ airway hyperresponsiveness[10]. It was previously believed that there might be pulmonary hyperinflation after repeated attack of moderate and severe asthma, latest research suggests there is also reduced lung function in mild asthma, and research on lung function in patients with CVA is less[11]. When CVA children are complicated with infection, both number and severity of disease attack also increase, they may lead to normal lung function damage, and therefore, the basic lung function levels of two groups were determined in the study. In addition to the basic lung function, small airway damage is an important feature of CVA patients, many studies have confirmed that maximum mid-expiratory flow (FEF_{25-75%}), an index representing small airway function, decreases significantly in patients with airway hyperresponsiveness, it is the decisive factor of airway sensitivity, and therefore, the values of three indexes that represented small airway function: maximum mid-expiratory flow (FEF_{25-75%}), mid-expiratory velocity (FEF_{50%}), late-expiratory velocity (FEF_{75%}) were further determined in the study. The study results showed that the levels of basic lung function indexes FEV1, and FVC as well as small airway function indexes MMEF, FEF_{50%} and FEF_{75%} of observation group significantly improved after treatment, indicating that azithromycin, terbutaline combined with montelukast can inhibit the inflammatory state in CVA children with infection and meanwhile help the optimization of the airway hyperresponsiveness.

Both CVA and bronchial asthma are the respiratory allergic diseases mediated by IgE, and eosinophil infiltration is their main pathological manifestation. Study shows that IgE positive rate in patients with CVA is as high as 40%-80%, so the IgE level can reflect the sensitization level in CVA patients to some extent, and high level of IgE is an important factor contributed to the airway allergic inflammation[12]. Eosinophil cationic protein (ECP) is the toxic protein released after acidophil is activated by antigen, it can cause respiratory epithelium damage and bronchial smooth muscle spasm contraction, and ECP is an important marker inducing and worsening asthma[13]. Interleukin-5 (IL-5) is produced by the activated CD4+ T lymphocytes (Th2), it has the important function of adjusting the eosinophil function, and it plays an important role in eosinophil activation and maturation, chemotaxis, recruitment to airway and other links. In addition to nonspecific inflammation, there is also extracellular matrix synthesis and degradation imbalance in children with CVA, which is airway remodeling. Matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) are the important rate-limiting enzymes of extracellular matrix metabolism in the process of airway remodeling[14,15]. MMP-2 and MMP-9 can promote the matrix degradation; TIMP-1 inhibits MMP-2 and MMP-9 activity and leads to the extracellular matrix deposition and airway remodeling, and the equilibrium state of the three factors will directly decide airway remodeling process in children with CVA. The study results showed that children with observation group after treatment serum ECP, IgE, IL-5, MMP-2, MMP-9 and TIMP-1 of observation group were lower after treatment, lower levels of ECP, IgE and IL-5 indicated that combined treatment reduced the airway sensitivity in CVA children with infection, and lower levels of MMP-2, MMP-9 and TIMP-1 indicated that the extracellular matrix degradation and deposition balance was effectively restored and the airway remodeling progression was suppressed.

C-reactive protein (CRP) is a non-specific acute phase protein produced by the liver, bacterial infection, acute rejection, cardiovascular disease and so on can all cause elevated CRP, and the index has rapid response but is short of specificity to infection. Procalcitonin (PET) is a precursor hormone of calcitonin, is a new inflammatory index to diagnose infection, and has strong specificity[16]. PET content is extremely low in healthy human body, when the body is infected by certain bacteria, PET levels can rise significantly in early stage. CVA is related to Th1/Th2 cell proportion and function imbalance, and in the case of severe CVA, Th1/Th2 deviates toward Th2. Interleukin-4 (IL-4) is generated by the Th2 cells, interferon-γ (IFN-γ ) is produced by Th1 cells, and there are high levels of IL-4 and low levels of IFN-γ in CVA children with infection[17]. Human β -defensin-1 (hBD-1) is an important innate immune molecule of the body, partial immune deficiency is an important cause of CVA, immune molecule levels in the body continue to reduce when infection is complicated, and hBD-1 levels are negatively correlated with the degree of infection and can indirectly reflect the body’s infection severity[18]. The study results showed that serum PET, CRP and IL-4 levels of observation group decreased after treatment while IFN-γ and hBD-1 levels increased, indicating that after azithromycin, terbutaline combined with montelukast treatment, the systemic inflammatory state reduced in CVA children with infection, and this was an important internal cause of relieved CVA.

To sum up, azithromycin, terbutaline combined with montelukast can improve airway function and gradient of infection in cough variant asthma children with infection, and it’s worth popularization and application in clinical practice in the future.

References


[3] Chen Jing-bo, Hu Hua-yuan, Zhang Shou-shan. Clinical Observation on Azithromycin Combined with Montelukast for the Treatment of


