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Effects of montelukast sodium combined with pidotimod on acute phase protein and immune function in children with acute bronchitis

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ABSTRACT

Objective: To observe the effects of montelukast sodium combined with pidotimod on acute phase protein (APP) and indexes of immunologic function in pediatric acute bronchitis treatment. **Methods:** A total of 180 cases children with acute bronchitis acted as research objects were randomly divided into control group (n=65) and observation group (n=63). On the basis of conventional therapy, control group was treated by plus pidotimod. On this base, observation group was treated with montelukast sodium. The changes of acute phase proteins (CRP, HP, a1-AAG and CER) and immune function ($CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$) levels before and after treatment were observed after 2 months. **Results:** Before treatment, CRP, HP, a1-AAG, CER, $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ levels of two groups had no statistically significant difference; CRP, HP, a1-AAG, CER, and $CD8^+$ levels of control and observation groups decreased significantly after treatment, the decreases of observation group were more obvious than that of control group, and the levels after treatment were significantly lower than that of control groups. The levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in two groups after treatment were significantly higher than those before treatment. For observation group, the levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ increased more significantly after treatment, which were significantly higher than that of the control group. **Conclusion:** Using Montelukast sodium combined with pidotimod can effectively reduce the children's acute phase protein levels, improve immune function, which has clinical value for the treatment of children with acute bronchitis.

1. Introduction

Acute bronchitis, bronchial mucosal inflammation namely, is an clinical disease of infants and young children, often complicates or secondary to upper respiratory tract infection, also has its clinical manifestations in pertussis, typhoid and other acute, infectious diseases. The main clinical manifestations of this disorder include cough, wheezing and difficulty breathing. This disorder are easy to repeat, causing serious adverse consequences like failure of breathing and heart, etc, seriously threat the life safety of afflicted children[1,2]. Cough expectorant, regulating immune function are the key to acute bronchitis treatment. Pidotimod, as a class of immunomodulatory drugs, can enhance immunity of the organism[3]. Montelukast sodium, a leukotriene receptor inhibitor, is an effective drug for reducing airway inflammation, airway spasm and so on[4]. This study aims to investigate the clinical efficacy of montelukast sodium combined with pidotimod in the treatment of pediatric acute bronchitis.

2. Research objects and methods

2.1. General information

A total of 128 cases of gouty patients from Sept. 2015 to Feb. 2017 in our hospital were selected as research objects. All the selected patients satisfied the diagnostic criteria of western medicine for

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acute bronchitis, standards refer to the relevant contents of Zhu Fu Tong Practical Pediatrics[5] and Pediatrics[6]. The patients were randomly divided into two groups, control group (n=65) and observation group (n=63). In control group, there were 42 males and 23 females, with ages of 2-13 years, duration of 1-7 d, and the mean duration of (2.59±0.25) d. In observation group, there were 39 males and 24 females, with ages of 2-12 years, duration of 1-7 d, and the mean duration of (2.57±0.30) d. The sex, age and duration of two groups were similar (P>0.05). The informed consent procedure complied with the relevant regulations and all children and their families are voluntarily join to the study.

2.2. Standards of selection

Inclusion criteria: (1) Patients are in line with western diagnostic criteria, with cough, short of breath and other symptoms; (2) Patients range in age from 1-14 years; (3) Body temperature of patients before entering the group do not exceed 38.5 ℃; (4) Physical examination shows that there are different degrees of moist rales in both lungs, wheezing and so on; (5) All the children and their families are informed consent, and signed consent forms voluntarily. Exclusion criteria[7]: (2) Patients in early pneumonia is difficult to be identify and patients with severe bronchitis; (2) Patients accompany with acute infectious diseases such as whooping cough, urticaria and other diseases; (3) Patients suffer from acute upper respiratory tract infection, bronchiolitis and acute exacerbation of chronic bronchitis and other respiratory diseases except for acute bronchitis; (4) Patients take the relevant drug treatments or allergic to investigational drugs; (5) Patients do not receive treatments or with poor compliance, can not finish the whole treatments and follow-up treatments; (6) Patients drop out, like medication cause severe disease (Stop medication immediately, take effective treatment) and patients bail out; (7) Patients with incomplete clinical data.

2.3. Therapeutic method

Two groups of patients were given conventional symptomatic treatments, such as anti-infection, anti-virus, antitussive, expectorant, relieving asthma, defervescence, oxygen uptake, etc. Based on the above treatments, the control group of patients were given pidotimod oral solution (Manufacturer: Jiangsu Wuzhong Pharmaceutical Group Corporation, Suzhou Pharmaceutical Factory, product batch number 2017011714), with initial dose of 400 mg/once, 2 times/d, and increasing to 400 mg/once, 1 times/d after 2 weeks. The observation group were given montelukast sodium (Manufacturer: UK. Merck Sharp & Dohme Ltd., product batch number J20130054) based on conventional treatments, with dose of 5 mg/once, 1 time/night, addition of pidotimod daily, the specific method refer to the control group. Both groups were treated for 2 months.

2.4. Observational indexes

3-5 mL of fasting peripheral venous blood of two group patients were collected before and after treatments. Blood serum was collected by centrifugation. Nephelometry was used to test the level of acute phase protein (APP): C-reactive protein (CRP), haptoglobin (HP), a1 acid glycoprotein (a1-AAG), cerocyanin (CER) and others. CRP level was tested by Siemens ADVIA1800 automatic biochemical analyzer. HP, a1-AAG and CER was tested by particular globin analyzer ADVIA1800, produced by Beckman Coulter. The levels of T lymphocytes ($CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$) were detected by BD FACSCalibur flow cytometry. The kit was selected according to the detecting instrument and the tested processes were performed according to the instructions.

2.5. Statistical analysis

SPSS 17.0 statistical package was conducted for statistical analysis. The level of each indicator in this study was in line with the normal distribution, which was described as ($\bar{x}$±s). Independent-samples t test was conducted to group comparisons as well as between comparisons, values of P<0.05 was considered to be statistically significant.

3. Results

3.1. Comparison of acute phase protein levels before and after treatment

The comparisons of CRP, HP, a1-AAG and CER levels in two groups before treatment were not statistically significant (P>0.05). After treatment, CRP, HP, a1-AAG and CER levels in control group were (5.33±0.49) mg/L, (2.81±0.29) mg/L, (1.64±0.52) mg/L and (584.72±70.83) mg/L, respectively, which were significantly decreased compared with that before treatment, which were considered to be statistically significant (P<0.05). After treatment, CRP, HP, a1-AAG and CER levels in observation group were (3.08±0.52) mg/L, (2.04±0.22) mg/L, (1.27±0.45) mg/L and (406.67±55.28) mg/L, respectively, significantly decreased and lower than that in control group, which were considered to be statistically significant (P<0.05). As shown in Table 1.

Table 1.

Comparison of acute phase protein levels before and after treatment.

Groups	n	Time	CRP (mg/L)	HP (mg/L)	a1-AAG (mg/L)	CER (mg/L)
Control group	65	Before treatment	8.90±0.82	4.25±0.32	4.57±0.80	812.07±88.51
		After treatment	5.33±0.49*	2.81±0.29*	1.64±0.52*	584.72±70.83*
Observation group	63	Before treatment	8.89±0.86	4.27±0.37	4.49±0.76	809.37±90.47
		After treatment	3.08±0.52$^{*\#}$	2.04±0.22$^{*\#}$	1.27±0.45$^{*\#}$	406.67±55.28$^\#$

Note: compared with group before treatment,$^*P$<0.05; compared with control group after treatment,$^\#P$<0.05.

Table 2.

Comparison of immune function indexes before and after treatment.

Groups	*n*	Time	$CD3^+$ (%)	$CD4^+$ (%)	CD8+ (%)	$CD4^+/CD8^+$
Control group	65	Before treatment	43.86±4.48	27.78±3.94	36.17±7.08	0.86±0.22
		After treatment	52.29±5.41*	33.07±5.21*	27.94±4.69*	1.07±0.36*
Observation group	63	Before treatment	43.29±4.66	27.92±3.87	35.84±7.11	0.87±0.29
		After treatment	61.17±5.93*#	39.06±6.14*#	22.91±3.02*#	1.28±0.21*#

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

3.2. Comparison of immune function indexes before and after treatment

The comparisons of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels in two groups before treatment were not statistically significant (P>0.05). After treatment, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels in control group and observation group were (52.29±5.41)%, (33.07±5.21)%, (1.07±0.36), (61.17±5.93)%, (39.06±6.14)% and (1.28±0.21), respectively, which were significantly increased compared with that before treatment, and the levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in observation group were significantly higher than that in control group (P<0.05). After treatment, $CD8^+$ level in observation group was (22.91±3.02)%, significantly decreased and lower than that in control group (27.94±4.69)%, which was considered to be statistically significant (P<0.05). As shown in Table 2.

4. Discussion

Pediatric acute bronchitis is a common respiratory disease in pediatrics, the incidence of pediatric respiratory disorder shows a higher risk due to the special physiological and anatomic structure of respiratory system and vulnerable immune function of children. This disease is caused by a bronchial mucosal inflammatory response which is initiated by inflammatory cell such as eosinophils and neutrophils, more secondary to upper tract respiratory infections. If the treatment is not timely or prompt, it may lead to pulmonary heart disease, emphysema and other serious complications, even threat to children's health[8,9]. The incidence of acute bronchitis is often accompany the occurrence of wheezing symptoms, and the mechanism of acute bronchitis is similar to asthma, namely airway smooth muscle contraction caused by a variety of inflammatory factors[10]. Clinical treatments of children with acute bronchitis often focus on control infection and symptomatic treatment. However, treatment for long periods of time may cause side effects and relapse because of its long duration and easily repeated after discontinuance[11].

Pidotimod is a chemically synthesized immunomodulatory drug, could promote specific immune response and non-specific immune response to a certain extent, which may enhance immunologic function, thereby promote the ability to fight infection, effectively improve the recurrence[12]. Montelukast sodium is a leukotriene receptor inhibitor, relevant studies showed that it can inhibit the inflammatory factors, cytokines and the release of respiratory leukotriene, etc, to improve the high airway response[13]. Related studies found that montelukast sodium can effectively shorten the treatment process of acute bronchitis, and effectively relief wheezing and other symptoms[14]. This study use pidotimod combined with montelukast sodium in the treatment of children with acute bronchitis, to investigate its clinical efficacy.

APP is a protein associating with the body's stress response. The synthesis of APP is linked closely to infection and tissue damage caused by inflammatory response[15]. Serum APP increases with different speed, when inflammation or tissue damage occurs, serum CRP levels rapidly increase within 4 to 6 hours after inflammatory reaction. Hence, CRP level, more sensitive and reliable, not only can be used as an APP test indicators, but also a valuable inflammatory marker to assess the degree of infection and prognosis[16]. Serum HP and a1-AAG levels increase slowly, and possess a long half-life. After treatment for about 12-20 d, the levels of HP and a1-AAG may return to normal[17]. HP is a sensitive intravascular hemolytic index, which can combine with hemoglobin and then participate in the anti-infection and tissue repair process. Also, the HP level significantly increases in patients with acute or chronic infections, trauma, burns and malignant tumors, which makes it can be used to assess the inflammatory state of the body[18]. After being stimulated by inflammatory, inflammatory factors will promote the release of large amounts of lipopolysaccharide from phagocytic cells, thereby accelerate the synthesis of a1-AAG. In the acute inflammatory response, a1-AAG is a sensitive inflammatory marker, the change of a1-AAG level in the body precedes temperature and white cell counts. Accordingly, a1-AAG level can be widely used as an importance evaluation index for clinical treatment and prognosis[19]. CER is a copper-containing 2 glycoprotein, related studies showed that CER had a certain antioxidant function. In the blood microcirculation, CER can hinder the synthesis of lipid peroxides and free radicals in the tissue, is of great significance in inflammation. The level of CER significantly increases in infection, trauma and tumor, which makes CER can be used as a diagnostic indicator of acute infection[20]. Related studies confirmed that APP can inhibit the accumulation of neutrophils and

platelets by regulating T lymphocytes and complement function, so as to improve the control of inflammatorystress response, enhance nonspecific resistance towards infections, and maintain the integrity of the organization[21] The results of this study showed that both treatments can effectively reduce the level of serum APP in patients, in addition, the efficacy of combination treatment was more significant. The results also showed that montelukast sodium combined with pidotimod treatment can effectively improve the level of serum APP, promote the regression of inflammation, which may due to the superposed inhibition of montelukast sodium combined with pidotimod towards inflammation.

In addition, the results of this study also showed that montelukast sodium combined with pidotimod on the regulation of immune function is significantly better than individual pidotimod treatment. The reason may be that as an immunomodulator, pidotimod can regulate immune function, which is the reason for combined treatment can improve immune function. Moreover, montelukast sodium can competitively antagonize the combination of leukotrienes and their receptors, blocking leukotriene on $CD8^+$ T cells to raise, reduce the inflammatory mediator chemotaxis effectively, inhibit inflammatory response, benefit to recovery[22].

In conclusion, montelukast sodium can improve children's lung function by reducing inflammatory response and therefore effectively relieve wheezing and other clinical symptoms. pidotimod can improve the immune function of children by immunoregulation, to enhance immunologic function. Using both of them for treatment of children with acute bronchitis, can effectively reduce the level of APP in serum, improve the immune function of children. The efficacy of montelukast sodium combined with pidotimod was significantly better than the individual pidotimod treatment, The treatment of montelukast sodium combined with pidotimod shows a certain clinical value.

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