Effect of creatine phosphate sodium combined with spleen amino peptide on hand-foot-mouth disease in children with myocardial damage

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ABSTRACT

Objective: To explore the clinical effect of creatine phosphate sodium combined with spleen aminopeptide on treatment of hand-foot-mouth disease in children with myocardial damage.

Methods: A total of 86 cases with hand-foot-mouth disease combined with cardiac damage in our hospital from January 2012 to July 2014 were randomly divided into the observation group and the control group with 43 cases in each group. Patients in the control group received conventional treatment while observation group patients were treated with creatine phosphate sodium combined with spleen amino peptide treatment. Hs-CRP, myocardial enzymes indexes, serum cytokines, NT-proBNP, PCT, endotoxin, D-lactate and immune related indicators were compared between two groups of children after treatment.

Results: In observation group patients' serum IL-4, IL-6 and IL-17 levels were lower than those of the control group after treatment (P<0.05) while IFN-γ and IL-10 levels were higher than those of the control group (P<0.05). In observation group patients' NT-proBNP, PCT, endotoxin and D-lactate levels were lower than those of the control group after treatment (P<0.05). In observation group patients' CD3+, CD4+ T lymphocytes, IgA, IgM and IgG levels were higher than those of the control group after treatment while CD8+ T lymphocyte level was lower than that of the control group (P<0.05).

Conclusions: Creatine phosphate sodium combined with spleen amino peptide treatment can effectively protect myocardial and regulate immune as well as optimize systemic inflammatory state.

1. Introduction

Hand-foot-mouth disease is a common viral infectious disease in children. It has a self-limited duration, but when the virus has a strong virulence or the children have weak immune system, important organ complication may occur[1,2]. Hand-foot-mouth disease with myocardial injury is a severe condition, which must be treated with aggressive clinical intervention. Creatine phosphate sodium is the most commonly used clinical drug for myocardial protection, and apart from direct energy supply, it can also regulate cardiac cells’ sodium-potassium-calcium channels and ensure the myocardial blood perfusion. Spleen amino peptide is a kind of immune modulator, which is rich in immune regulatory factors and essential amino acids of human body, and whose effect of strengthening the immune function has been approved[3]. This study mainly analyzed the clinical effect and mechanism of creatine phosphate sodium combined with spleen amino peptide treatment of hand-foot-mouth disease in children with myocardial damage.

2. Materials and methods

2.1. Clinical data

A total of 86 cases with hand-foot-mouth disease combined with cardiac damage in our hospital from January 2012 to July 2014 were randomly divided into the observation group and the control group with 43 cases in each group. In the control group, there were
23 male cases and 20 female cases, they were 1-9 years old and the average was (4.79±0.65) years old. In the observation group, there were 22 males and 21 females, they were 1-8 years old and the average was (4.65±0.71) years old. Two groups of children were with no significant difference in baseline data (P>0.05), and they were comparable.

2.2. Treatment methods

The control group received conventional therapy as follows: ribavirin injection at a dose of 10 mg/(kg·d), 2 times a day, a total of 5 days.

The observation group received conventional treatment combined with sodium phosphocreatine and spleen aminopeptide as follows: adding 1 g sodium phosphocreatine to 50 mL physiological saline, intravenous infusion, once a day; taking spleen aminopeptide freeze dry 2 mg orally, once daily. Both drugs were continuously used for a week.

2.3. Observation indexes

Peripheral venous blood of children was collected after treatment and centrifuged to get serum samples for detection of the following indexes. Levels of high sensitive C-reactive protein (hs-CRP) were determined by immune scatter turbidimetry. Myocardial enzymes, including creatine kinase (CK) and isoenzyme (CK-MB), troponin I (cTn-I), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (A-HBDS) and aspartate aminotransferase (AST) were tested by full automatic analyzer. Enzyme linked immunosorbent assay (ELISA) was used for the determination of serum interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-10 (IL-10) and NT-proBNP levels. The modified substrate azo colorimetric method was used for determination of endotoxin levels and the enzyme spectrophotometry was used for the determination of D-lactate level. Procalcitonin (PCT) level was tested by immunity speed scattering turbidimetric method. The levels of cellular immunity (CD3+, CD4+ T cell) and humoral immunity (IgA, IgM, IgG) were measured by the immune scattering turbidimetric assay.

2.4. Statistical methods

Data in this paper was input and statistically analyzed by SPSS 23.0 software. t-test was applied to the measurement data. P<0.05 was set as the standard of statistical significant differences.

3. Results

3.1. hs–CRP and myocardial enzyme indexes

The results showed that compared with the control group, serum hs-CRP, CK, CK-MB, Ctn I, LDH, A-HBDS and AST levels were lower in the observation group of patients after treatment (P<0.05), shown in Table 1.

3.2. Serum cytokines

Serum IL-4, IL-6, IL-25 and IL-17 values of observation group after treatment were lower than those of the control group while IFN-γ and IL-10 values were higher than those of the control group (P<0.05), shown in Table 2.

3.3. NT-proBNP, PCT, endotoxin, D–lactate

The results showed that the serum NT-proBNP, PCT, endotoxin and D-lactate values were lower in the observation group after treatment than those in the control group patients (P<0.05), as shown in Table 3.

3.4. Immunity–related indicators

The results showed that CD3+, CD4+ T cells, IgA, IgM and IgG values were higher in the patients of the observation group after treatment than those in the patients of the control group while the level of CD8+ T lymphocytes was lower (P<0.05), shown in Table 4.

4. Discussion

Hand-foot-mouth disease is the most common infectious disease in children, whose course is acute but mostly self-limited. Some severe
cases may complicate with myocardial damage. Patients with hand-foot-mouth disease and myocardial damage should accept positive anti-viral treatment and also treatment of myocardial protection to avoid the occurrence of permanent cardiac function damage and reduce the probability of long-term myocarditis[4,5]. Creatine is clinically commonly used exogenous drug, which can effectively maintain the ATP level in the body and protect myocardial fiber membrane against ischemic damage. Creatine phosphate sodium can affect the heart ion channels of sodium, calcium and potassium, and maintain normal cardiac electrophysiological activity in the state of ischemia and hypoxia. Creatine phosphate sodium can also improve the physiological status of vascular epithelial cells, loose platelets, increase hypoxic red cells’ plasticity, increase penetration resistance of red blood cells, improve the microcirculation of the heart and protect the normal perfusion of children’s heart. Spleen amino peptide is a kind of immune regulator, which has a function in the treatment of low cellular immune function and immunodeficiency disease. It has been successfully used in the treatment of bronchitis, pneumonia and asthma patients[6].

Hand-foot-mouth disease patients with myocardial damage must accept positive interventions, and except anti-viral therapy, myocardial protection and immune supportive treatment must be added. The study added creatine phosphate sodium combined with splenic aminopeptidase in the observation group of patients. Myocardial injury indexes, inflammatory factors and immune factors were studied. Hand-foot-mouth disease-associated virus can directly act on the cardiac muscle cells and lead to occurrence of necrosis and inflammatory reaction. The body’s immune response can aggravate the damage of myocardial cells too[7,8]. Hs-CRP is an acute phase protein synthesized by the liver cells, which can activate the complement system and the immune regulation after polymerized with bacteria. Hs-CRP level is not affected by whole blood, hormones or drugs, so it is more objective and credible. It has been confirmed that the levels of myocardial enzymes in children with hand-foot-mouth disease are significantly increased, and the degree of rise is proportional to the severity of the disease. CK-MB has the highest content in cardiac muscle cells and can be released into the blood in the early stage of cardiac muscle cell damage, which is a specific index to judge the myocardial injury of the children[9]. CTnI is also a common index of myocardial enzymes, the specificity of which is higher than that of CK-MB, and the sensitivity is lower. So the results are more reliable when combined with other myocardial enzyme indexes. LDH is a kind of glucoytic enzyme, which can catalyze lactic acid dehydrogenate into pyruvic acid. LDH contains five types of isoenzyme, which can be used to diagnose diseases according to tissue specificity. When the myocardial enzymes are released into the blood, LDH1 > LDH2, and can diagnose heart disease according to this. A-HBDS is not an independent specific enzyme, which can reflect the activity of lactate dehydrogenase isoenzyme, and has positive significance for the diagnosis of myocardial disease. When acute myocardial infarction and other myocardial injury disease occur, the level increases significantly. The study detected myocardial enzyme spectrum levels in children and found that: hs-CRP, CK, CK-MB, CTnI, LDH, A-HBDS and AST levels were lower in observation group of patients after treatment, suggesting that creatine phosphate sodium combined with spleen amino peptide treatment could effectively reduce the myocardial enzyme indicator levels and play a role in myocardial protection.

Children with hand-foot-mouth disease have significant systemic inflammatory response, which is worse when complicated with myocardial injury, and will further lead to increased myocardial damage, and form a vicious circle. IL-6 is an important mediator of inflammation and immune regulation factor. IL-10 has a strong anti-inflammatory and immune activity-inhibiting effect, which inhibits mononuclear macrophages induce inflammatory factor, and also has anti-virus effect. Levels of IL-6 and IL-10 can represent the balance between inflammation and anti-inflammation. IL-25 is a newly discovered cytokine secreted by Th2 cells, which can induce IL-4 and IL-6 production, and up-regulate the expression of eosinophils. IL-17 is mainly produced by Th17 cells, which can induce monocyte macrophage. Endothelial cells produce a variety of proinflammatory factors, which further activates inflammatory reaction and complement. Th1 cell’s normal function relies on IFN-γ while Th2 cell depends on IL-4. In cases of hand-foot-mouth disease combined with myocardial damage, Th2 cell leads a dominant role in the body and produces a large number of IL-4 to inhibit TNF-γ function[10,11]. The research results showed that IL-4, IL-6, IL-25 and IL-17 levels were lower in observation group of patients after treatment while IFN-γ and IL-10 levels were higher, suggesting that antiretroviral combined with myocardial protection and immune regulation therapy was helpful to decrease systemic inflammatory response in children.

BNP is a kind of cardiac hormone secreted by the heart chamber, which is synthesized and secreted when damage or overload occurs.

Table 3

Comparison of NT-proBNP, PCT, endotoxin and D-lactate levels in serum after treatment between groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>NT-proBNP (pg/mL)</th>
<th>PCT (ng/L)</th>
<th>Endotoxin (EU/L)</th>
<th>D-lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>103.27±8.95</td>
<td>45.82±4.06</td>
<td>24.72±2.53</td>
<td>1.27±0.13</td>
</tr>
<tr>
<td>Control group</td>
<td>176.39±14.25</td>
<td>67.31±5.97</td>
<td>53.91±4.98</td>
<td>1.86±0.15</td>
</tr>
<tr>
<td>t</td>
<td>8.945</td>
<td>7.283</td>
<td>8.923</td>
<td>6.837</td>
</tr>
<tr>
<td>P</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 4

Comparison of serum immunity-related indexes after treatment between groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>CD3⁺T cell</th>
<th>CD4⁺T cell</th>
<th>CD8⁺T cell</th>
<th>IgA (g/L)</th>
<th>IgG (g/L)</th>
<th>IgM (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>54.12±4.65</td>
<td>27.75±2.67</td>
<td>16.09±1.53</td>
<td>1.27±0.15</td>
<td>1.31±0.12</td>
<td>9.14±0.87</td>
</tr>
<tr>
<td>Control group</td>
<td>49.35±4.09</td>
<td>24.33±2.47</td>
<td>21.23±2.42</td>
<td>0.93±0.08</td>
<td>0.89±0.07</td>
<td>7.09±0.58</td>
</tr>
<tr>
<td>t</td>
<td>7.293</td>
<td>5.323</td>
<td>7.182</td>
<td>6.938</td>
<td>6.938</td>
<td>8.712</td>
</tr>
<tr>
<td>P</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>
to the heart. Before synthesizing BNP, cardiac cells first synthesize BNP precursor (proBNP), proBNP (NT-proBNP) has no activity and a longer half-life in the blood. In cases of cardiac damage, NT-proBNP rises more significantly than BNP. Therefore, NT-proBNP can accurately reflect the early changes in cardiac function, and is an effective indicator of myocardial injury[12]. Calcitonin (PCT) is a calcitonin peptide that has no hormone activity, which can be converted into calcitonin in the body and play a variety of biological functions. In normal human, serum PCT content is very low, but under the pathological state, PCT is continuously released and plays an important role in the process of inflammatory reaction, which can be used as a new indicator of clinical evaluation of infection[13]. Endotoxin is the main component of gram-negative bacterial cell wall. In cases of intestinal dysfunction, it moves into blood and causes blood endotoxin level rise. D-lactate is a metabolic product of the indigenous flora in gastrointestinal tract, and its serum level can accurately reflect the intestinal mucosal integrity and overall damage of the children. Studies have shown that when children with hand-foot-mouth disease are complicated with other important organ dysfunction, the endotoxin and D-lactate levels are significantly increased, and are proportional to the severity of the complications. The research results showed that serum NT-proBNP, PCT, endotoxin and D-lactate levels were lower in observation group of patients after treatment, suggesting that creatine phosphate sodium combined with spleen amino peptide therapy protected myocardium, enhanced immune function and contributed to the recovery of the disease.

Spleen amino peptide is a multifunctional immune enhancing agent, which is extracted from the spleen of healthy animals, rich in essential trace elements and immune regulating factors, and has a significant effect on enhancing immune function. The immune function in children with hand-foot-mouth disease is significantly abnormal, including cellular immunity and humoral immunity. The further decline of the immune function is also closely related to the final myocardial damage[14]. CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes are the main cells of cellular immunity, CD3<sup>+</sup>T cell level represents the overall function of cellular immunity, CD4<sup>+</sup> T cell is the helper T cell and CD8<sup>+</sup> is called cytotoxic T cell. Humoral immunity is an important part of the body’s specific immunity, which can stimulate the body to produce specific antibodies such as IgA, IgM, IgG and so on. IgA has antiviral effect, which is an important barrier to defense pathogen invasion[15]. IgM is one of the earliest immune globulins in the humoral immune response, and is one of the indicators of early diagnosis of hand-foot-mouth disease. IgG can neutralize free exotoxins and virus, which is the only immune globulin in gastrointestinal tract, and its serum level can get through the placental barrier, and participate in the immune defense. The above research results showed that CD3<sup>+</sup> and CD4<sup>+</sup> T lymphocytes as well as IgA, IgG and IgM levels were higher in observation group of patients after treatment, and CD8<sup>+</sup> T lymphocyte level was lower. This indicated that the addition of splenic aminopeptidase significantly enhanced the immune function of children and had positive significance for the final rehabilitation of children’s disease.

To sum up, we can draw the following conclusions: creatine phosphate sodium combined with spleen amino peptide treatment can play an effective role in myocardial protection and immune regulatory in children of hand-foot-mouth disease complicated with myocardial injury, which also optimizes systemic inflammatory state, and is worthy to be popularized in the future clinical practice.

References