Study on the protective effect of adenosine cyclophosphate combined with vitamin C antiviral therapy on myocardial injury in children with viral myocarditis

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ABSTRACT

Objective: To study the protective effect of adenosine cyclophosphate combined with vitamin C antiviral therapy on myocardial injury in children with viral myocarditis. Methods: 88 cases of children with viral myocarditis treated in Ningde Hospital of Traditional Chinese Medicine of Fujian University of Traditional Chinese Medicine between June 2014 and September 2016 were selected and randomly divided into the intervention group and the control group who received adenosine cyclophosphate combined with vitamin C antiviral therapy and conventional therapy respectively. Serum levels of myocardial injury indexes, antioxidant indexes and collagen metabolism indexes were determined. Results: 1 week and 2 weeks after treatment, serum LDH, CK, CK-MB, ET-1, Ang-II, PICP and PINP contents of both groups were significantly lower than those before treatment while SOD, GSH-Px, CAT and HO-1 contents were significantly higher than those before treatment and serum LDH, CK, CK-MB, ET-1, Ang-II, PICP and PINP contents of intervention group were significantly lower than those of control group while SOD, GSH-Px, CAT and HO-1 contents were significantly higher than those of control group. Conclusion: Adenosine cyclophosphate combined with vitamin C therapy for viral myocarditis can reduce myocardial injury and improve collagen metabolism.

1. Introduction

Viral myocarditis is the most common pediatric disease of the cardiovascular system, and the common pathogens include Coxsackie virus, adenovirus, ECHO virus, influenza virus, etc[1,2]. The anti-infection immune response mechanism development is immature in pediatric population, the virus replicates itself easily in the body after infection, and the pathological characteristics of children with viral myocarditis are direct damage of virus and its toxins to the myocardium as well as the myocardial oxidative stress damage of calcium overload and massive production of oxygen free radicals to the myocardium after virus infection[3]. In clinical practice, antivirus, myocardial nutrition, improving myocardial oxygen supply and inhibiting myocardial oxygen consumption are routine treatments. Adenosine cyclophosphate and vitamin C are the drugs that have been used for treatment of myocardial ischemic disease in recent years, the former is an important second messenger in the body and can participate in the regulation of matter and energy metabolism and improve the myocardial cell metabolism, and the latter is a water-soluble vitamin with antioxidant properties and can reduce the damage of calcium ion overload and massive generation of oxygen free radicals to the myocardial cells[4]. In the following studies, the protective effect of adenosine cyclophosphate combined with vitamin C antiviral therapy on myocardial injury in children with viral myocarditis was analyzed.
2. Clinical information and research methods

2.1 Clinical information

Children with viral myocarditis treated in Ningde Hospital of Traditional Chinese Medicine of Fujian University of Traditional Chinese Medicine between June 2014 and September 2016 were selected as the research subjects, all children were in accordance with the diagnosis for viral myocarditis, and the children with congenital heart disease, rheumatic heart disease and tuberculosis pericarditis were excluded. A total of 88 patients with viral myocarditis were enrolled and randomly divided into two groups, each with 44 cases. The intervention group included 25 male cases and 19 female cases that were 7-12 years old; the control group included 24 male cases and 20 female cases that were 6-12 years old. There was no significant difference in the general data between the two groups (\(P>0.05\)).

2.2 Drug therapy

Both groups of patients were given oxygen uptake, water and electrolyte balance and acid-base balance adjustment, ribavirin for antivirus, coenzyme Q10 for myocardial nutrition and other conventional treatment, anti-arrhythmic treatment was provided according to the arrhythmia during the course, and cardiotonic, diuretic and vascular dilation therapy were provided if there might be heart failure. Intervention group, on the basis of routine therapy, received adenosine cyclophosphate and vitamin C treatment, and the method was as follows: adenosine cyclophosphate 1 mg/kg in 250 mL of saline, by intravenous drip, 1 time/d; Vitamin C 175 mg/kg in 250 mL of saline, intravenous drip, 1 time/d. Treatment lasted for 2 weeks.

2.3 Myocardial injury index detection methods

Before treatment as well as 1 week and 2 weeks after treatment, 2 mL peripheral venous blood was collected from two groups of patients respectively, let stand for coagulation and then centrifuged to separate supernatant, fully automatic biochemical analyzer was used to detect lactate dehydrogenase (LDH), creatine kinase (CK) and creatine kinase isoenzyme (CK-MB) content, radioimmunoprecipitation kit was used to detect superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) and heme oxygenase (HO-1) content, and enzyme-linked immunosorbent assay kit was used to detect endothelin-1 (ET-1), angiotensin-II (Ang-II), C-terminal propeptide of procollagen type I (PICP) and N-terminal propeptide of procollagen type I (PI NP) content.

2.4 Statistical methods

SPSS 17.0 software was used to input serum detection data, analysis of serum detection data between two groups as well as before and after treatment was by t test, and \(P<0.05\) indicated statistical significance in differences.

3. Results

3.1 Serum myocardial injury marker contents of two groups of children

Before treatment as well as 1 week and 2 weeks after treatment, analysis of serum myocardial injury markers LDH, CK and CK-MB contents between two groups of children was as follows: before treatment, serum LDH, CK and CK-MB contents were not significantly different between two groups of children (\(P>0.05\)); 1 week and 2 weeks after treatment, serum LDH, CK and CK-MB contents of both groups were significantly lower than those before treatment (\(P<0.05\)) and serum LDH, CK and CK-MB contents of intervention group were significantly lower than those of control group (\(P<0.05\)).

3.2 Serum anti-oxidation index contents of two groups of children

Before treatment as well as 1 week and 2 weeks after treatment, analysis of serum anti-oxidation indexes SOD, GSH-Px, CAT and HO-1 contents between two groups of children was as follows: before treatment, serum SOD, GSH-Px, CAT and HO-1 contents of intervention group were significantly lower than those of control group (\(P<0.05\)).

Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>LDH</th>
<th>CK</th>
<th>CK-MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>44</td>
<td>Before treatment</td>
<td>364.21±52.59</td>
<td>224.71±32.95</td>
<td>41.29±6.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 week after treatment</td>
<td>215.68±33.63*</td>
<td>127.58±17.74*</td>
<td>20.18±3.62*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks after treatment</td>
<td>168.51±22.36*</td>
<td>78.59±9.34*</td>
<td>13.57±1.96*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before treatment</td>
<td>366.25±51.26</td>
<td>225.42±31.28</td>
<td>42.08±6.28</td>
</tr>
<tr>
<td>Control</td>
<td>44</td>
<td>1 week after treatment</td>
<td>289.75±36.26*</td>
<td>178.93±22.15*</td>
<td>29.58±4.27*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks after treatment</td>
<td>221.35±33.12*</td>
<td>126.62±17.29*</td>
<td>21.42±3.68*</td>
</tr>
</tbody>
</table>

*: differences were statistically significant between intervention group and control group, \(P<0.05\); #: differences were statistically significant within group before treatment and after treatment, \(P<0.05\).
(P<0.05); 1 week and 2 weeks after treatment, serum SOD, GSH-Px, CAT and HO-1 contents of both groups were significantly higher than those before treatment (P<0.05) and serum SOD, GSH-Px, CAT and HO-1 contents of intervention group were significantly higher than those of control group (P<0.05).

3.3 Serum collagen metabolism index contents of two groups of children

Before treatment as well as 1 week and 2 weeks after treatment, analysis of serum collagen metabolism indexes ET-1 (ng/mL), Ang-II (pg/mL), PICP (ng/mL) and PINP (ng/mL) contents between two groups of children was as follows: before treatment, serum ET-1, Ang-II, PICP and PINP contents were not significantly different between two groups of children (P>0.05); 1 week and 2 weeks after treatment, serum ET-1, Ang-II, PICP and PINP contents of both groups were significantly lower than those before treatment (P<0.05) and serum ET-1, Ang-II, PICP and PINP contents of intervention group were significantly lower than those of control group (P<0.05).

4. Discussion

Viral myocarditis is the myocardial injury caused by the Coxsackie virus, adenovirus, ECHO virus, influenza virus, and so on. After the myocardial cells are infected by virus, the virus itself and the toxins synthesized by it can both cause myocardial cell damage; the massive viral replication can cause calcium overload and the massive production of oxygen free radicals in the local tissue, which cause myocardial cell damage by oxidative stress. Although conventional antiviral and myocardial nutritional treatment will inhibit viral replication and reduce myocardial cell damage to a certain degree, there are still some children with poor curative effect and prognosis[5–7]. Adenosine cyclophosphate and vitamin C are drugs that have been used for treatment of myocardial ischemic diseases in recent years. Adenosine cyclophosphate is an important second messenger in the body, which can adjust the material and energy metabolism in the myocardial cells, reduce the preload and afterload of the cardiac contraction, and help to reduce myocardial cell injury; Vitamin C is a water-soluble vitamin with antioxidant effect, which can reduce the production of oxygen free radicals in cells, inhibit the ROS attack to intracellular lipid composition, and thus reduce oxidative stress damage to myocardial cells[8,9].

In the study, adenosine cyclophosphate and vitamin C were used for the treatment of children with viral myocarditis so as to play the role of adenosine cyclophosphate in improving myocardial cell metabolism and the role of vitamin C in resisting oxidative stress damage. Myocardial cells will rupture under the action of direct damage factors and indirect damage factor of oxidative stress, and many kinds of catalyzing enzymes involved in cell energy and substance metabolism in the cytoplasm will be released into the blood circulation, and then become the marker molecules that reflect myocardial cell damage degree. In order to define the value of adenosine cyclophosphate combined with vitamin C therapy for viral myocarditis, serum myocardial enzymes LDH, CK and CK-MB contents were analyzed at first in the study to reflect the damage degree of myocardial cells. Comparison of serum myocardial enzyme levels between two groups of children showed that serum LDH, CK and CK-MB contents of both groups after treatment were significantly lower than those before treatment and serum LDH, CK and CK-MB contents of intervention group after treatment were significantly lower than those of control group. This means that conventional treatment can reduce the degree of myocardial injury of children with viral myocarditis, and combination of adenosine cyclophosphate and vitamin C can improve the treatment effects and further reduce the degree of myocardial injury.

Table 2.

Comparison of serum anti-oxidation indexes before and after treatment (U/L).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>SOD</th>
<th>GSH-Px</th>
<th>CAT</th>
<th>HO-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>44</td>
<td>Before treatment</td>
<td>56.2±8.97</td>
<td>46.2±6.28</td>
<td>35.2±6.24</td>
<td>17.5±1.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 week after treatment</td>
<td>85.2±10.25</td>
<td>73.1±5.62</td>
<td>58.7±7.31</td>
<td>34.2±6.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks after treatment</td>
<td>112.5±14.85</td>
<td>105.8±14.57</td>
<td>76.5±9.42</td>
<td>53.5±7.52</td>
</tr>
<tr>
<td>Control</td>
<td>44</td>
<td>Before treatment</td>
<td>57.0±9.12</td>
<td>45.6±7.49</td>
<td>34.6±5.98</td>
<td>18.1±2.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 week after treatment</td>
<td>69.8±9.25</td>
<td>59.1±7.53</td>
<td>44.1±5.96</td>
<td>24.5±2.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks after treatment</td>
<td>78.7±9.36</td>
<td>68.7±9.25</td>
<td>57.2±8.24</td>
<td>37.4±5.62</td>
</tr>
</tbody>
</table>

*: differences were statistically significant between intervention group and control group, P<0.05; #: differences were statistically significant within group before treatment and after treatment, P<0.05.

Table 3.

Comparison of serum collagen metabolism indexes before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>ET-1</th>
<th>Ang-II</th>
<th>PICP</th>
<th>PINP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>44</td>
<td>Before treatment</td>
<td>125.2±17.84</td>
<td>91.3±11.25</td>
<td>164.4±20.32</td>
<td>67.6±9.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 week after treatment</td>
<td>62.1±7.85</td>
<td>42.4±6.72</td>
<td>103.5±14.67</td>
<td>38.5±5.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks after treatment</td>
<td>40.2±6.53</td>
<td>29.3±4.21</td>
<td>68.9±9.52</td>
<td>25.5±4.59</td>
</tr>
<tr>
<td>Control</td>
<td>44</td>
<td>Before treatment</td>
<td>127.0±18.49</td>
<td>92.1±11.98</td>
<td>165.6±21.39</td>
<td>68.1±9.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 week after treatment</td>
<td>89.4±11.25</td>
<td>76.5±9.35</td>
<td>137.6±22.31</td>
<td>49.3±8.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks after treatment</td>
<td>62.4±8.49</td>
<td>44.2±5.68</td>
<td>97.4±11.26</td>
<td>37.5±6.28</td>
</tr>
</tbody>
</table>

*: differences were statistically significant between intervention group and control group, P<0.05; #: differences were statistically significant within group before treatment and after treatment, P<0.05.
Oxidative stress damage caused by excessive generation of oxygen free radicals is a significant indirect factor to cause myocardial cell damage in children with viral myocarditis. The production of oxygen free radicals is related to oxidative stress caused directly by the virus and toxin, and is also associated with the abnormal electro transport process of the mitochondrial respiratory chain. There are various antioxidant enzymes in myocardial cells, which can remove the oxygen free radicals overproduced in the process of oxidative stress[10,11]. SOD and GSH-Px can directly reduce the oxygen free radicals and generate hydrogen peroxide, CAT can further reduce the hydrogen peroxide into water molecules and discharge them, and HO-1 is involved in multiple links of the oxygen free radical removal [12]. Adenosine cyclrophosphate can improve the energy and substance metabolism of myocardial cells and inhibit the production of oxygen free radicals; Vitamin C has direct antioxidant activity and can remove oxygen free radicals. Decreased generation and increased removal of oxygen free radicals can reduce oxidative stress reaction damage to myocardial cells, and also reduce the consumption of SOD, GSH-Px, CAT, HO-1 and other antioxidant enzymes during oxidative stress damage. In the study, the analysis of serum contents of these antioxidant enzymes showed that serum SOD, GSH-Px, CAT and HO-1 contents of both groups after treatment were significantly higher than those before treatment and serum SOD, GSH-Px, CAT and HO-1 contents of intervention group after treatment were significantly higher than those of control group. This shows that the combination of adenosine and vitamin C can inhibit the oxidative stress response in children with viral myocarditis.

In the development of viral myocarditis, the myocardial fibrosis that is caused by excessive collagen proliferation in myocardial matrix after infection will affect the disease outcome. ET-1 and Ang-II are the important molecules participating in myocardial fibrosis and promoting the proliferation of collagen in matrix. The myocardial cell damage in children with viral myocarditis will cause local ischemia hypoxia, thereby increasing the release of ET-1 and Ang-II. ET-1 can directly promote the proliferation of smooth muscle cells and the increase of extracellular matrix synthesis; Ang-II can be combined with the receptor AT1R to promote fibroblast proliferation and collagen synthesis[13,14]. PICP and PINP are the products during the type I collagen synthesis, and they can reflect the activity of collagen synthesis[15,16]. In the study, analysis of the contents of myocardial remodeling and collagen metabolism indexes showed that serum ET-1, Ang-II, PICP and PINP contents of both groups after treatment were significantly lower than those before treatment and serum ET-1, Ang-II, PICP and PINP contents of intervention group after treatment were significantly lower than those of control group. This shows that the combination of adenosine and vitamin C can improve collagen metabolism and inhibit myocardial remodeling in children with viral myocarditis.

To sum up, it is believed that adenosine cyclophosphate combined with vitamin C therapy for children with viral myocarditis can reduce myocardial cell injury and inhibit oxidative stress reaction, and can also improve myocardial matrix collagen metabolism and inhibit myocardial fibrosis.

References