Effect of ulinastatin on the plasma neuroendocrine factor in patients with chronic heart failure

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OBJECTIVE: To analyze the therapeutic effect of ulinastatin in the treatment of chronic heart failure (CHF) and the effect on the plasma neuroendocrine factor. METHODS: A total of 78 patients with CHF who were admitted in our hospital were included in the study and randomized into the observation group and the control group. The patients in the two groups were given routine anti-heart-failure treatments. On this basis, the patients in the observation group were given ulinastatin injection, continuously for 7 d. The serum inflammatory cytokines, plasma neuroendocrine factors, and T lymphocyte subsets before and after treatment were detected. Echocardiography was performed before and after treatment. The cardiac function indicators in the two groups were compared. RESULTS: The serum CRP, IL-6, and TNF-α, and plasma BNP, ANP, ET, and β2-MG after treatment in the two groups were significantly reduced when compared with before treatment (P<0.05), and those in the observation group were significantly lower than those in the control group (P<0.05). IL-10 after treatment in the observation group was significantly higher than that in the control group (P<0.05). LVESD and LVEDD after treatment in the two groups were significantly reduced when compared with before treatment (P<0.05), while LVEF was significantly increased (P<0.05). LVEF after treatment in the observation group was significantly higher than that in the control group (P<0.05). CD4+/CD8+ after treatment in the two groups was not significantly changed when compared with before treatment (P>0.05), while CD4+ was significantly elevated (P<0.05), and CD8+ was significantly reduced (P<0.05), and the comparison between the two groups was statistically significant (P<0.05). CD4+/CD8+ after treatment in the observation group was significantly higher than that in the control group (P<0.05). Conclusions: Routine treatment in combined with ulinastatin injection can significantly inhibit the excessive activation of neuroendocrine factors in patients with CHF, enhance the cellular immune function, alleviate the inflammatory reaction, and promote the recovery of cardiac function, with a significant efficacy.

1. Introduction

Chronic heart failure (CHF) is the terminal development results of most cardiovascular disease, and is also the main reason for causing death in patients with cardiovascular disease. It is found that the excessive expression of serum pro-inflammatory cytokines in patients with CHF can induce the myocardial cell apoptosis and fibrosis, promote the ventricular remodeling, and accelerate the heart failure progression. Some scholars argue that various neuroendocrine cytokines, such as ANP, BNP, and ET, are closely associated with the occurrence and development of heart failure[1,2]. Ulinastatin is a kind of glycoprotein extracted from the urine, can significantly inhibit the activity of various enzymes, alleviate the immunological damage caused by the inflammatory mediators, and is widely applied in the treatment of CHF, but its effect on the neuroendocrine in patients with CHF is less reported[3]. The study is aimed to explore the effect of ulinastatin on the serum inflammatory cytokines, plasma neuroendocrine factors, cardiac function, and cellular immunity.
2. Materials and methods

2.1. Clinical materials

A total of 78 patients with CHF who were admitted in our hospital from March, 2015 to February, 2016 were included in the study and randomized into the observation group and the control group with 39 cases in each group. In the observation group, 20 were male, and 19 were female; aged from 45 to 79 years old; 12 at grade II, 19 at grade III, and 8 at grade IV according to NYHA grading. In the control group, 21 were male, and 18 were female; aged from 45 to 80 years old; 11 at grade II, 21 at grade III, and 7 at grade IV according to NYHA grading. The patients were in accordance with the related diagnostic criteria of CHF in the Diagnosis and Treatment Guideline of CHF[4]. The comparison of gender, age, and NYHA grading between the two groups was not statistically significant (P>0.05), but it was comparable. Exclusion criteria: (1) those who were allergic to related studied drugs; (2) those who were accompanied by sick sinus syndrome or II-III degree atrioventricular block; (3) those who were accompanied by severe mental disorders; (4) those who were merged with severe bronchial asthma.

2.2. Methods

The patients in the two groups were given routine anti-heart-failure treatments, including cardiotonic, diuretics, vasodilator substance, and β-receptor blocker, oxygen inhalation, restriction on the sodium and salt intake, and electrolyte disturbance and acid-base imbalance correcting. On this basis, the patients in the observation group were given ulinastatin injection (produced by Guangdong Temple Biochemical Pharmaceutical Co. Ltd, Approval No. H20040506, 2 mL: 100 000U), 400 000U by micro pump infusion + 10% glucose (50 mL), 1 h/time, 2 times/d. The patients in the two groups were continuously treated for 7 d.

2.3. Observation indicators

A volume of 5 mL fasting venous blood before and after treatment in the two groups was collected. ELISA was used to detect the serum CRP, IL-6, IL-10, and TNF-α. RIA was used to detect the plasma BNP, ANP, ET, and β2-MG. FCM was used to detect CD3+, CD4+, and CD8+. CD4+/CD8+ was calculated. Philips cardiovascular dedicated color Doppler ultrasound was used to detect LVEDD, LVESD, and LVEF before and after treatment in order to evaluate the cardiac function.

2.4. Statistical analysis

SPSS 13.0 software was used for the statistical analysis. The measurement data were expressed as mean±SD. The paired t test was used for the intra-group comparison, while the independent t test was used for the comparison between the two groups. P<0.05 was regarded as statistically significant.

3. Results

3.1. Comparison of the serum inflammatory cytokines before and after treatment between the two groups

The serum CRP, IL-6, and TNF-α after treatment in the two groups were significantly reduced when compared with before treatment (P<0.05), and those in the observation group were significantly lower than those in the control group (P<0.05). IL-10 after treatment in the observation group was significantly higher than that in the control group (P<0.05) (Table 1).

3.2. Comparison of the plasma neuroendocrine factors before and after treatment between the two groups

The plasma BNP, ANP, ET, and β2-MG after treatment in the observation group were significantly reduced when compared with before treatment (P<0.05), and were significantly lower than those in the control group (P<0.05). IL-10 after treatment in the observation group was significantly higher than that in the control group (P<0.05) (Table 2).

3.3. Comparison of the cardiac function indicators before and after treatment between the two groups

LVESD and LVEDD after treatment in the two groups were significantly reduced when compared with before treatment (P<0.05), while LVEF was significantly increased (P<0.05). LVEF

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>CRP</th>
<th>IL-6</th>
<th>IL-10</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>6.3±2.0</td>
<td>274.1±14.6</td>
<td>81.3±3.3</td>
<td>79.3±7.4</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>2.4±1.7*</td>
<td>121.3±14.5*</td>
<td>90.8±4.2*</td>
<td>28.7±6.8*</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>6.4±2.1</td>
<td>275.3±13.9</td>
<td>80.9±4.7</td>
<td>78.1±6.7</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>3.9±1.8*</td>
<td>231.1±11.7</td>
<td>82.5±5.0</td>
<td>57.6±7.9*</td>
</tr>
</tbody>
</table>

*P<0.05, when compared with before treatment; #P<0.05, when compared with the control group.
after treatment in the observation group was significantly higher than that in the control group ($P<0.05$) (Table 3).

### 3.4. Comparison of T lymphocyte subsets before and after treatment between the two groups

$CD^+_8$ after treatment in the two groups was not significantly changed when compared with before treatment ($P>0.05$), while $CD^+_4$ was significantly elevated ($P<0.05$), and $CD^+_8$ was significantly reduced ($P<0.05$), and the comparison between the two groups was statistically significant ($P<0.05$). $CD^+_3/CD^+_8$ after treatment in the observation group was significantly higher than that in the control group ($P<0.05$) (Table 4).

## 4. Discussion

Inflammation is a main factor for promoting the occurrence and development of CHF, and has accepted widespread concern by numerous scholars. Some researches demonstrate that[5] the levels of inflammatory cytokines in patients with CHF are significantly higher than those in the normal individuals. Ulinastatin, as a kind of natural inflammatory reaction regulatory substance, can significantly inhibit the activation of neutrophils and monomacrophages, block the release of inflammatory mediators, and the cascade reaction of inflammatory cytokines, restrain the excessive activation of leukocytes, and prevent the vicious circle among the cytokines, inflammatory mediators, and leukocytes[6]. CRP is a marker to reflect the inflammatory reaction intensity in the myocardial tissues. IL-6 and IL-10 are the serum pro-inflammatory cytokine and anti-inflammatory cytokine, respectively, are involved in the inflammatory reaction and immune response, and can regulate the occurrence and development of inflammation. IL-6, IL-10, and TNF-α can be served as the inflammatory markers to affect the severity degree of heart failure[6,7]. The results in the study showed that the serum CRP, IL-6, and TNF-α after treatment in the two groups were significantly reduced when compared with before treatment ($P<0.05$), and those in the observation group were significantly lower than those in the control group ($P<0.05$), indicating that ulinastatin can down regulate the pro-inflammatory cytokines, up regulate the anti-inflammatory cytokines, improve the myocardial inflammation, and alleviate the clinical symptoms[8,9].

CHF is closely associated with the excessive activation of RAAS and sympathetic neuroendocrine system. BNP is a sensitive indicator to evaluate the cardiac function and prognosis in patients with CHF. Due to the reduced cardiac output and elevated ventricular end-diastolic pressure in patients with CHF, the atrial volume and pressure are increased, which can act on the atrial wall receptor to increase the release of ANP by the atrial cells; moreover, the elevated systemic circulation and pulmonary circulation resistance, and cardiac remodeling can significantly elevate the plasma ET level, especially ET-1 level[10,11]. In addition, the cardiac output in

### Table 2

Comparison of the plasma neuroendocrine factors before and after treatment between the two groups ($\bar{x}\pm s, n=39$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>BNP</th>
<th>ANP</th>
<th>ET</th>
<th>$\beta$-MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>887.5±7.4</td>
<td>224.2±8.6</td>
<td>87.1±8.7</td>
<td>6.1±1.5</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>501.3±6.2 *</td>
<td>202.7±8.7 *</td>
<td>49.9±10.5 *</td>
<td>4.1±2.0 *</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>884.7±5.8</td>
<td>222.4±8.2</td>
<td>86.2±9.1</td>
<td>5.9±2.2</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>934.5±7.1 *</td>
<td>211.2±8.4 *</td>
<td>82.6±10.3</td>
<td>4.9±1.4 *</td>
</tr>
</tbody>
</table>

$P<0.05$, when compared with before treatment; *$P<0.05$, when compared with the control group.

### Table 3

Comparison of the cardiac function indicators before and after treatment between the two groups ($\bar{x}\pm s, n=39$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>LVEDD</th>
<th>LVEDD</th>
<th>LVESD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>37.6±6.3</td>
<td>43.6±8.1</td>
<td>39.8±12.3</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>29.2±6.8 *</td>
<td>38.2±8.0 *</td>
<td>54.5±13.3 *</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>37.3±7.2</td>
<td>43.5±8.2</td>
<td>40.3±12.2</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>31.6±6.6 *</td>
<td>39.3±8.2 *</td>
<td>47.6±13.5 *</td>
</tr>
</tbody>
</table>

$P<0.05$, when compared with before treatment; *$P<0.05$, when compared with the control group.

### Table 4

Comparison of T lymphocyte subsets before and after treatment between the two groups ($\bar{x}\pm s, n=39$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>CD4 +</th>
<th>CD4 +</th>
<th>CD8 +</th>
<th>CD3 +/CD4 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>62.9±8.7</td>
<td>33.2±6.3</td>
<td>23.3±4.6</td>
<td>1.6±0.4</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>62.6±9.0</td>
<td>41.7±5.8 *</td>
<td>19.1±4.3 *</td>
<td>1.9±0.3 *</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>63.0±8.3</td>
<td>32.1±5.9</td>
<td>23.4±4.7</td>
<td>1.6±0.3</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>63.5±8.5</td>
<td>35.8±6.1</td>
<td>21.1±3.9 *</td>
<td>1.7±0.4</td>
</tr>
</tbody>
</table>

$P<0.05$, when compared with before treatment; *$P<0.05$, when compared with the control group.
patients with CHF is reduced, and the renal perfusion is decreased, resulting in pre-renal renal function damage, which can affect the serum β2-MG metabolism, leading to the reduced discharge of β2-MG. The blood and urine β2-MG content is gradually increased with the aggravation of heart failure degree[12]. The results in the study showed that the plasma BNP, ANP, ET, and β2-MG after treatment in the observation group were significantly reduced when compared with before treatment (P<0.05), and were significantly lower than those in the control group (P<0.05); LVEF after treatment in the two groups were significantly reduced when compared with before treatment (P<0.05), while LVEF was significantly increased (P<0.05); LVEF after treatment in the observation group was significantly higher than that in the control group (P<0.05), indicating that ulinastatin can significantly reduce the left ventricular chamber inner diameter in patients with CHF, alleviate the cardiac load, improve the cardiac function, promote β2-MG metabolism, and improve the renal function along with the cardiac function[13,14]. T lymphocytes are the important immune cells. CD4⁺ and CD8⁺ are mutually affected and restricted, resulting in the body in a relative balance state. It is reported that[15,16] CD4⁺ and CD8⁺ in patients with CHF are significantly reduced with the damage of cardiac function. The results in the study showed that CD4⁺ after treatment in the two groups was not significantly changed when compared with before treatment (P>0.05), while CD4⁺ was significantly elevated (P<0.05), and CD8⁺ was significantly reduced (P<0.05), and the comparison between the two groups was statistically significant (P<0.05); CD4⁺/CD8⁺ after treatment in the observation group was significantly higher than that in the control group (P<0.05), indicating that ulinastatin can significantly enhance the cellular immunological function in patients with CHF.

In conclusion, routine treatment in combined with ulinastatin injection can significantly inhibit the excessive activation of neuroendocrine factors in patients with CHF, enhance the cellular immune function, alleviate the inflammatory reaction, and promote the recovery of cardiac function, with a significant efficacy.

References