Effect of Xuebijing combined with ulinastatin on the homeostasis of sepsis patients
Wei Chen

Department of Critical Care Medicine, Chengdu Third People's Hospital in Sichuan Province, Chengdu, Sichuan Province, 610041, China

ARTICLE INFO

Objective: To investigate the effect of Xuebijing combined with ulinastatin on the homeostasis of sepsis patients. Methods: 78 patients with post-burn sepsis who received treatment in our hospital between January 2016 and January 2019 were included in the study. The treatment regimen was retrospectively analyzed and used to divide the patients into the group A (n=40) receiving ulinastatin treatment and the group B (n=38) receiving Xuebijing combined with ulinastatin treatment. The efficacy was evaluated after 7 d of continuous treatment. Results: Before treatment, there were no significant differences in levels of inflammatory factors, oxidative stress indicators, myocardial injury markers or coagulation function indicators between the two groups. After treatment, serum high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) contents in group B were lower than those in group A; serum total antioxidant capacity (T-AOC) and glutathione peroxidase (GSH-Px) contents were higher than those in group A, while lipid hydroperoxide (LHP) and advanced protein oxidation product (AOPP) contents were lower than those in group A; serum lactate dehydrogenase (LDH), troponin I (cTn I) and B-type brain natriuretic peptide (BNP) contents were lower than those in group A; peripheral blood prothrombin time (PT), thrombin time (TT) and partial thromboplastin time (APTT) levels were higher than those in group A, while fibrinogen (FIB) level was lower than that in group A. Conclusion: Xuebijing combined with ulinastatin can effectively reduce the inflammatory stress response, actively protect the myocardial function and reduce the hypercoagulable state in patients with post-burn sepsis.

1. Introduction

Sepsis is a systemic inflammatory response syndrome caused by infection and is the body’s reaction to infectious factors. Sepsis is a dangerous disease with a very high fatality rate. Currently, the conventional treatment methods such as anti-shock, anti-infection and correction of water and electrolyte disorder have limitations in improving the prognosis of sepsis[1-3]. Ulinastatin is a glycoprotein that can inhibit the activity of a variety of proteolytic enzymes. It has an inhibitory effect on serine protease, hyaluronidase, sulfhydrase and other enzymes, and can also reduce the production of myocardial inhibitory factors. It has been successfully applied in the treatment of acute pancreatitis[4] and acute circulatory failure[5]. Xuebijing is a traditional Chinese medicine extract with antagonistic effect on endotoxin, which can be used for the treatment of multiple organ dysfunction caused by infection and burns. Therefore, it is recommended for clinical patients with sepsis after burns. In this paper, Xuebijing combined with ulinastatin was used for the treatment of post-burn sepsis patients in our hospital to explore the feasibility of this treatment scheme.

2. Data and methods

2.1 General data

78 patients with post-burn sepsis were treated in our hospital
between January 2016 and January 2019. The treatment regimen was retrospectively analyzed and used to divide the patients into the group A (n=40) receiving ulinastatin treatment and the group B (n=38) receiving Xuebijing combined with ulinastatin treatment. Group A included 22 males and females, were 45-71 years old and had APACHE II score of 25-32 (27.94±4.05) points; Group B included 20 males and 18 females, were 43-72 years old and had APACHE II score of 24-33 (27.58±4.17) points. The differences in age, gender or APACHE II score were not statistically significant between the two groups of patients (P>0.05), and they were comparable.

Inclusion criteria: (1) in accordance with the definition of sepsis in the “China Treatment Guidelines for Severe Sepsis / Septic Shock (2014)”[6] formulated by the Society of Critical Care Medicine, Chinese Medical Association; (2) diagnosed with sepsis for the first time and receiving no relevant treatment; (3) < 80 years old; (4) without previous treatment history of Xuebijing or ulinastatin; (5) whose immediate family members signed the informed consent. Exclusion criteria: (1) complicated with coronary heart disease, valvular heart disease, pulmonary heart disease or other basic cardiac diseases; (2) complicated with malignant tumor diseases; (3) complicated with autoimmune diseases; (4) highly allergic to Xuebijing or ulinastatin.

2.2 Treatment methods

Both groups of patients received routine treatment including fluid infusion, anti-infection, correcting water and electrolyte disorders, vasoactive drugs, nutritional support and respiratory support. Group A were treated with ulinastatin on the basis of conventional treatment, which was specifically as follows: ulinastatin for injection (produced by Guangdong Techpool Bio-Pharma Co., Ltd., batch number 20171019) in normal saline, by intravenous infusion, 200 000 IU/time and 2 times/d. Group B received Xuebijing treatment on the basis of that for group A, which was as follows: Xuebijing injection (produced by Tianjin Chase Sun Pharmaceutical Co., Ltd., batch number 20180317), by intravenous infusion, 50 mL/time and 2 times/d. Both groups were evaluated for efficacy after 7 d of continuous treatment.

2.3 Observation indicators

Peripheral venous blood samples of the two groups of patients were collected before and after treatment, and the serum was isolated and stored for later use. ELISA kits were used to determine serum contents of (1) inflammatory cytokines: high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), (2) oxidative stress indexes: total antioxidant capacity (T-AOC), glutathione peroxidase (GSH-Px), lipid hydroperoxide (LHP) and advanced protein oxidation product (AOPP) as well as (3) myocardial injury markers: lactate dehydrogenase (LDH), troponin I (cTn I) and B-type brain natriuretic peptide (BNP). Peripheral venous blood samples were also taken to determine the levels of coagulation indexes by Beckman ACL7000 automatic coagulation analyzer, including prothrombin time (PT), thrombin time (TT), partial thrombin time (APTT) and fibrinogen (FIB).  

2.4 Statistical method

The software was SPSS 21.0, and the difference was statistically significant if P<0.05. The two groups of measurement data conformed to the normal distribution and had same homogeneity of variance, and the comparison was conducted by t test.

3. Results

3.1 Comparison of inflammatory factor contents

Before treatment, there were no statistically significant differences in serum hs-CRP (mg/L), IL-6 (pg/mL), IL-8 (pg/mL) or TNF-α (pg/mL) contents between the two groups (P>0.05). After treatment, serum hs-CRP, IL-6, IL-8 and TNF-α contents in both groups were lower than those before treatment, the decline of above indicator contents was bigger in group B, and the differences were statistically significant (P<0.05), shown in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>hs-CRP (mg/L)</th>
<th>IL-6 (pg/mL)</th>
<th>IL-8 (pg/mL)</th>
<th>TNF-α (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>40</td>
<td>Before treatment</td>
<td>65.38±7.10</td>
<td>12.37±1.45</td>
<td>20.46±1.88</td>
<td>13.40±1.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>27.66±4.53</td>
<td>7.88±1.92</td>
<td>12.13±1.55</td>
<td>8.95±0.97</td>
</tr>
<tr>
<td>Group B</td>
<td>38</td>
<td>Before treatment</td>
<td>64.79±6.58</td>
<td>12.29±1.38</td>
<td>20.51±2.47</td>
<td>13.21±1.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>19.25±2.17</td>
<td>5.16±0.57</td>
<td>9.08±1.12</td>
<td>5.66±0.71</td>
</tr>
</tbody>
</table>

*P<0.05 compared with the same group before treatment. *P<0.05 compared with group A. *P<0.05 compared with group B.

Table 1. Comparison of serum inflammatory factor contents between the two groups (x±s).
3.2 Comparison of oxidative stress indicator contents

Before treatment, there were no statistically significant differences in serum T-AOC (U/L), GSH-Px (mg/L), LHP (μmol/L) or AOPP (μmol/L) contents between the two groups (P>0.05). After treatment, serum T-AOC and GSH-Px contents in both groups were higher than those before treatment, while LHP and AOPP contents were lower than those before treatment, the change of above indicator contents was bigger in group B, and the differences were statistically significant (P<0.05), shown in Table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>T-AOC</th>
<th>GSH-Px</th>
<th>LHP</th>
<th>AOPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>40</td>
<td>Before treatment</td>
<td>19.74±2.18</td>
<td>43.27±6.10</td>
<td>28.46±3.19</td>
<td>102.57±14.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>27.58±3.19</td>
<td>58.31±7.49</td>
<td>20.12±2.54</td>
<td>70.11±8.95</td>
</tr>
<tr>
<td>Group B</td>
<td>38</td>
<td>Before treatment</td>
<td>19.68±2.05</td>
<td>43.58±5.76</td>
<td>28.55±5.04</td>
<td>101.99±15.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>34.66±5.09</td>
<td>70.88±9.21</td>
<td>13.19±1.52</td>
<td>48.66±6.21</td>
</tr>
</tbody>
</table>

3.3 Comparison of myocardial injury marker contents

Before treatment, there were no statistically significant differences in serum LDH (U/L), cTnl (μg/L) or BNP (pg/mL) contents between the two groups (P>0.05). After treatment, serum LDH, cTnl and BNP contents in both groups were lower than those before treatment, the decline of above indicator contents was bigger in group B, and the differences were statistically significant (P<0.05), shown in Table 3.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>LDH</th>
<th>cTnl</th>
<th>BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>40</td>
<td>Before treatment</td>
<td>549.37±62.11</td>
<td>2.19±0.27</td>
<td>1 532.48±175.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>372.08±42.66</td>
<td>1.38±0.16</td>
<td>930.21±121.66</td>
</tr>
<tr>
<td>Group B</td>
<td>38</td>
<td>Before treatment</td>
<td>550.64±59.83</td>
<td>2.16±0.29</td>
<td>1 517.62±169.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>260.99±31.18</td>
<td>1.10±0.15</td>
<td>548.36±69.22</td>
</tr>
</tbody>
</table>

3.4 Comparison of coagulation indicator levels

Before treatment, there were no statistically significant differences in peripheral blood PT (s), TT (s), APTT (s) or FIB (g/L) levels between the two groups (P>0.05). After treatment, peripheral blood PT, TT and APTT levels in both groups were higher than those before treatment while FIB levels were lower than those before treatment, the change of above indicator contents in group B was bigger than that in group A, and the differences were statistically significant (P<0.05), shown in Table 4.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>PT (s)</th>
<th>TT (s)</th>
<th>APTT (s)</th>
<th>FIB (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>40</td>
<td>Before treatment</td>
<td>9.20±0.98</td>
<td>18.45±2.10</td>
<td>25.48±3.12</td>
<td>7.58±0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>10.01±1.03</td>
<td>20.71±2.85</td>
<td>31.17±2.49</td>
<td>5.20±0.68</td>
</tr>
<tr>
<td>Group B</td>
<td>38</td>
<td>Before treatment</td>
<td>9.13±0.97</td>
<td>18.36±2.45</td>
<td>25.37±2.98</td>
<td>7.46±0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>11.02±1.28</td>
<td>23.48±3.01</td>
<td>34.32±2.15</td>
<td>4.37±0.52</td>
</tr>
</tbody>
</table>

4. Discussion

Burns are one of the important causes of sepsis. A large number of inflammatory factors are secreted in the body and gradually form an inflammatory cascade reaction, which further causes multiple organ impairment and eventually leads to multiple organ dysfunction syndrome (MODS) and even death[7,8]. Systemic inflammatory responses are the basis for the occurrence and development of sepsis.
hs-CRP, IL-6, IL-8 and TNF-α are the most commonly studied inflammatory factors at present, which have been confirmed to be highly expressed in the circulating blood of sepsis patients[9,10]. In this study, the contents of the above inflammatory factors in both groups showed a downward trend after treatment, indicating the effectiveness of the two treatment regimens. Meanwhile, the contents of the above indicators in group B showed a more significant decline, indicating that the addition of Xuebijing on the basis of ulinastatin can further inhibit the systemic inflammatory response in patients with sepsis.

Oxidative stress reaction and inflammatory reaction exist together, and they interact as both cause and effect and form a vicious cycle. Persistent inflammation in patients with sepsis has prompted the synthesis and secretion of a large number of oxygen free radicals and further leads to the accumulation of lipid metabolites LHP and AOPP. When antioxidants T-AOC and GSH-Px are excessively consumed, the body’s oxidative stress degree increases rapidly, which stimulates the aggravation of inflammatory response in patients with sepsis, and eventually leads to the aggravation of sepsis[11-13]. In this paper, serum LHP and AOPP contents in both groups of patients decreased while T-AOC and GSH-Px contents increased after treatment, and the change of above index contents in group B was more significant, it indicates that Xuebijing combined with ulinastatin can more effectively relieve the systemic oxidative stress response in patients with post-burn sepsis, and this may be closely related to the effect of the treatment plan in reducing the body's inflammatory response.

Studies[14,15] have found that more than 50% of patients with sepsis can be associated with myocardial injury, which is mainly manifested as arrhythmia and refractory heart failure, and is also one of the most important causes of death in patients with sepsis. Myocardial cells are highly susceptible to toxins, and the accumulation of various metabolites in the body of patients with sepsis, together with the impact of severe inflammatory stress response, leads to ischemic hypoxic injury of myocardial cells[16-18]. Various myocardial injury markers in serum can sensitively reflect the existence and specific severity of myocardial injury. In the study, serum myocardial injury markers LDH, cTn I and BNP contents in both groups were declining after treatment, they were even lower in group B, it indicates that Xuebijing combined with ulinastatin can effectively reduce the degree of myocardial injury in patients with sepsis, and this is one of the inevitable results of the plan to reduce the inflammatory stress response in the patients.

The inflammatory stress response in patients with sepsis can activate the coagulation system and cause the body to be in a hypercoagulable state, which may lead to subsequent thrombotic events[19,20]. The shortening of PT, TT and APTT as well as the increase of FIB level is the sign of the body’s hypercoagulable state. In this paper, PT, TT and APTT in both groups of patients were prolonged while FIB levels were reduced after treatment, and the change of above coagulation index levels was bigger in group B, indicating that Xuebijing combined with ulinastatin can more effectively inhibit the abnormal hypercoagulable state and effectively restore the body’s blood coagulation function in patients with sepsis. Therefore, Xuebijing combined with ulinastatin therapy on the basis of routine treatment can effectively reduce the inflammatory stress response and myocardial injury, also inhibit the hypercoagulable state and strongly restore the homeostasis in patients with post-burn sepsis.

References


[10] Qiao ZH, Shang ZB. The effects of ulinastatin on plasma levels of PCT...


