Effect of Xuebijing combined with early continuous renal replacement therapy on systemic inflammatory response and renal impairment in patients with heat stroke

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ABSTRACT

Objective: To study the effect of Xuebijing combined with early continuous renal replacement therapy on systemic inflammatory response and renal impairment in patients with heat stroke.

Methods: A total of 24 patients with heat shock who were treated in Qidong People’s Hospital between June 2015 and August 2017 were selected and divided into two groups, Xuebijing group received Xuebijing combined with early continuous renal replacement therapy, and control group received early continuous renal replacement therapy. Serum levels of inflammatory response cytokines, coagulation-related cytokines and renal function indicators of two groups of patients were detected before treatment as well as 3 d and 6 d after treatment.

Results: Serum TNF-α, IL-6, IL-17, hs-CRP, TF, sTM, sE-selectin, BUN, Scr, β2-MG and Cys-C levels of both groups 3 d and 6 d after treatment were significantly lower than those before treatment, and serum TNF-α, IL-6, IL-17, hs-CRP, TF, sTM, sE-selectin, BUN, Scr, β2-MG and Cys-C levels of Xuebijing group 3 d and 6 d after treatment were significantly lower than those of control group.

Conclusion: Xuebijing combined with early continuous renal replacement therapy can reduce the degree of systemic inflammatory response and renal impairment in patients with heat stroke.

1. Introduction

Heat stroke is the most severe type of heatstroke, which is characterized by the heat-regulating center dysfunction, and can lead to high fever, consciousness disorder and multiple organ dysfunction[1,2]. Systemic inflammatory response syndrome activation is an important pathological change in the course of the heat stroke, and the massively generated inflammatory cytokines can on the one hand, cause systemic multiple organ damage by inflammatory reaction, and on the other hand, also destroy the coagulation-antiocoagulation balance to affect tissue microcirculation and cause tissue damage. The kidney is a common target organ in the course of heat stroke sickness, and the renal function injury can cause the toxic metabolites to accumulate in the body. Continuous renal replacement therapy (CRRT) is used in critical illness treatment in recent years, which removes the inflammatory cytokines and adverse metabolites through the exchange of displacement fluid and human blood, and can reduce the viscera function damage in the course of a variety of critical diseases[3]. Xuebijing is a traditional Chinese medicine with anti-inflammatory and antiplatelet function, and is used for treating diseases such as kidney failure and sepsis[4]. In the following studies, we analyzed the effect of Xuebijing combined with early continuous renal replacement therapy on systemic inflammatory response and renal impairment in patients with heat stroke.

2. Case information and research methods

2.1. General case information

A total of 24 patients with heat shock who were treated in Qidong People’s Hospital between June 2015 and August 2017 were selected as the research subjects, and all of the patients were with acute onset, had the symptom such as high fever, dehydration, disturbance of consciousness and acute renal failure, and were with normal heart, liver and kidney function in the past. Patients
with autoimmune disease history and combined with malignant tumor were excluded. Random number table was used to divide the 24 patients with heat stroke into two groups, each with 12 cases. Xuebijing group included 7 men and 5 women that were 22-49 years old; control group included 8 men and 4 women that were 21-45 years old. There was no significant difference in general information between the two groups ($P>0.05$).

2.2 Therapy

Both groups of patients received fasting, physical cooling, parenteral nutrition support, massive rehydration, acidosis correction and other therapies immediately after admitted to hospital, and accepted continuous renal replacement therapy at the same time, and the method was as follows: extracorporeal circulation was founded after catheter indwelling via femoral vein puncture, hemofiltration machine was connected, the blood flow was set to 150-200 mL/min, replacement liquid flow rate to 2 000 mL/h and dialysate flow rate to 1 000 mL/h, and daily ultrafiltration was kept at 2 500-3 000 mL. Xuebijing group, on the basis of the above routine treatment, received Xuebijing therapy, and the method was as follows: Xuebijing injection 100 mL added in saline 50 mL, by intravenous drip, 2/d, for 3 d in a row.

2.3 Serum index detection

Before treatment and 3 d and 6 d after treatment, 3-5 mL of cubital venous blood was collected from the two groups respectively, let stand for stratification and then centrifuged to separate upper serum, enzyme-linked immunosorbent assay kit was used to determine serum TNF-$\alpha$, IL-6, IL-17, hs-CRP, TF, sTM, sE-selectin, $\beta$-2-MG and Cys-C levels, and automatic biochemical analyzer was used to determine BUN and Scr levels.

### 2.4 Statistical methods

SPSS 21.0 software was used to input serum test indexes, differences in indexes between two groups were analyzed by t test and $P<0.05$ indicated statistical significance in differences in test results.

3. Results

3.1 Serum inflammatory response cytokine levels

Before treatment and 3 d and 6 d after treatment, analysis of serum inflammatory response cytokines TNF-$\alpha$ (ng/L), IL-6 (ng/L), IL-17 (ng/L) and hs-CRP (mg/L) levels between two groups of patients was as follows: serum TNF-$\alpha$, IL-6, IL-17 and hs-CRP levels were not significantly different between two groups of patients before treatment ($P>0.05$); serum TNF-$\alpha$, IL-6, IL-17 and hs-CRP levels of both groups 3 days and 6 d after treatment were significantly lower than those before treatment ($P<0.05$), and serum TNF-, IL-6, IL-17 and hs-CRP levels of Xuebijing group 3 d and 6 d after treatment were significantly lower than those of control group ($P<0.05$).

### Table 1

**Changes in serum inflammatory response cytokines before and after treatment.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>TNF-$\alpha$</th>
<th>IL-6</th>
<th>IL-17</th>
<th>hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xuebijing</td>
<td>12</td>
<td>Before</td>
<td>272.1±32.5</td>
<td>149.5±18.5</td>
<td>9.31±1.15</td>
<td>22.52±3.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>104.4±14.2*</td>
<td>82.5±9.5*</td>
<td>4.52±0.56*</td>
<td>8.61±0.94*</td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>Before</td>
<td>274.1±33.6</td>
<td>151.0±17.3</td>
<td>9.27±1.04</td>
<td>22.18±2.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>178.1±20.4*</td>
<td>117.5±14.6</td>
<td>7.71±0.94*</td>
<td>13.21±1.55*</td>
</tr>
</tbody>
</table>

*: comparison of indexes within group between before and after treatment, $P<0.05$; #: comparison of indexes between Xuebijing group and control group after treatment, $P<0.05$.

### Table 2

**Changes in serum coagulation-related cytokines before and after treatment.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>TF</th>
<th>sTM</th>
<th>sE-selectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xuebijing</td>
<td>12</td>
<td>Before</td>
<td>452.1±57.5</td>
<td>128.5±15.8</td>
<td>252.4±33.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>226.3±32.6*</td>
<td>76.3±9.3*</td>
<td>98.3±10.4*</td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>Before</td>
<td>450.9±53.7</td>
<td>130.1±14.6</td>
<td>250.9±31.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>324.2±41.9*</td>
<td>93.5±11.4*</td>
<td>142.1±17.9*</td>
</tr>
</tbody>
</table>

*: comparison of indexes within group between before and after treatment, $P<0.05$; #: comparison of indexes between Xuebijing group and control group after treatment, $P<0.05$. 

**2.2 Therapy**

**3. Results**

**3.1 Serum inflammatory response cytokine levels**

Before treatment and 3 d and 6 d after treatment, analysis of serum inflammatory response cytokines TNF-$\alpha$ (ng/L), IL-6 (ng/L), IL-17 (ng/L) and hs-CRP (mg/L) levels between two groups of patients was as follows: serum TNF-$\alpha$, IL-6, IL-17 and hs-CRP levels were not significantly different between two groups of patients before treatment ($P>0.05$); serum TNF-$\alpha$, IL-6, IL-17 and hs-CRP levels of both groups 3 days and 6 d after treatment were significantly lower than those before treatment ($P<0.05$), and serum TNF-, IL-6, IL-17 and hs-CRP levels of Xuebijing group 3 d and 6 d after treatment were significantly lower than those of control group ($P<0.05$).

**3.2 Serum coagulation-related cytokine levels**

Before treatment and 3 d and 6 d after treatment, analysis of serum coagulation-related cytokines TF (ng/L), sTM (μg/L) and sE-selectin (ng/L) levels between two groups of patients was as follows: serum TF, sTM and sE-selectin levels were not significantly different between two groups of patients before treatment ($P>0.05$); serum TF, sTM and sE-selectin levels of both groups 3 d and 6 d after treatment were significantly lower than those before treatment ($P<0.05$), and serum TF, sTM and sE-selectin levels of Xuebijing group 3 d and 6 d after treatment were significantly lower than those of control group ($P<0.05$).
The heat stroke is critically ill, progresses rapidly, and can develop to systemic inflammatory response syndrome and multiple organ dysfunction syndrome in a short time. The rate of disability and mortality are both high. The occurrence of heat stroke is closely related to the heat-regulating center disorder, sweat gland failure as well as disturbance of water and electrolyte caused by high temperature and high humidity environment; persistent disturbance of water and electrolyte can further activate systemic inflammatory response, cause massive release of inflammatory mediators, and then increase the risk of multiple organ dysfunction syndrome. CRRT is a common therapy for patients with end-stage renal disease, which removes toxic metabolites from the body through exchange between replacement fluid and human blood. In recent years, the therapy is increasingly used in the treatment of sepsis, severe acute pancreatitis and other critical diseases, which can remove the inflammatory cytokines massively produced in the course of disease and alleviate the inflammation so as to reduce systemic multiple organ function damage[5,6]. Excessive inflammatory reaction activation is the key link causing heat stroke progression and multiple viscera function damage, and the use of CRRT can effectively remove inflammatory cytokines, reduce inflammation reaction and improve the condition of heat stroke[7]. Xuebijing is a Chinese medicine preparation of critical diseases, which contains the active components of Ligusticum wallichii, salvia miltiorrhiza, safflower, red paony root and other traditional Chinese medicines, and has the pharmacological effects such as inhibiting the secretion of inflammatory factors, resisting platelet aggregation and improving microcirculation and tissue perfusion[8,9].

Table 3. Changes in serum renal function indexes before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Scr</th>
<th>BUN</th>
<th>β2-MG</th>
<th>Cys-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xuebijing</td>
<td>12</td>
<td>Before treatment</td>
<td>294.5±33.1</td>
<td>38.6±5.5</td>
<td>5.62±0.74</td>
<td>2.93±0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>156.4±17.8*</td>
<td>17.5±2.2*</td>
<td>3.14±0.37*</td>
<td>1.14±0.15*</td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>Before treatment</td>
<td>295.2±29.4</td>
<td>39.4±5.7</td>
<td>5.58±0.68</td>
<td>3.01±0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>202.2±25.6</td>
<td>27.1±3.5*</td>
<td>4.21±0.35*</td>
<td>1.89±0.22*</td>
</tr>
</tbody>
</table>

*: comparison of indexes within group between before and after treatment, P<0.05; *: comparison of indexes between Xuebijing group and control group after treatment, P<0.05.

4. Discussion

The heat stroke is critically ill, progresses rapidly, and can develop to systemic inflammatory response syndrome and multiple organ dysfunction syndrome in a short time. The rate of disability and mortality are both high. The occurrence of heat stroke is closely related to the heat-regulating center disorder, sweat gland failure as well as disturbance of water and electrolyte caused by high temperature and high humidity environment; persistent disturbance of water and electrolyte can further activate systemic inflammatory response, cause massive release of inflammatory mediators, and then increase the risk of multiple organ dysfunction syndrome. CRRT is a common therapy for patients with end-stage renal disease, which removes toxic metabolites from the body through exchange between replacement fluid and human blood. In recent years, the therapy is increasingly used in the treatment of sepsis, severe acute pancreatitis and other critical diseases, which can remove the inflammatory cytokines massively produced in the course of disease and alleviate the inflammation so as to reduce systemic multiple organ function damage[5,6]. Excessive inflammatory reaction activation is the key link causing heat stroke progression and multiple viscera function damage, and the use of CRRT can effectively remove inflammatory cytokines, reduce inflammation reaction and improve the condition of heat stroke[7]. Xuebijing is a Chinese medicine preparation of critical diseases, which contains the active components of Ligusticum wallichii, salvia miltiorrhiza, safflower, red paony root and other traditional Chinese medicines, and has the pharmacological effects such as inhibiting the secretion of inflammatory factors, resisting platelet aggregation and improving microcirculation and tissue perfusion[8,9].

In recent years, the value of Xuebijing for heat stroke has received more and more attention[10]. In this study, Xuebijing combined with CRRT was used to treat the heat stroke so as to play the roles of Xuebijing in inhibiting inflammatory response, anti-platelet and improving microcirculation. TNF-α, IL-6, IL-17 and hs-CRP are inflammatory cytokines closely associated with the activation of inflammatory response in patients with heat stroke[11,12]; TNF-α changes in the early stage of inflammatory response and has a trigger and amplification effect on inflammatory response; IL-6 has a variety of biological functions and plays the role of chemokines in the process of inflammatory reaction[13]; IL-17 is a cytokine secreted by Th17, which can cause inflammatory tissue injury; hs-CRP is an acute phase protein produced by liver cells under the action of pro-inflammatory cytokines, which is consistent with the degree of inflammation. In order to define the effect of Xuebijing combined with CRRT on systemic inflammatory response activation in patients with heat stroke, serum levels of above inflammatory cytokine were analyzed before and after treatment, and the results showed that serum TNF-α, IL-6, IL-17 and hs-CRP levels of both groups significantly decreased after treatment, and serum TNF-α, IL-6, IL-17 and hs-CRP levels of Xuebijing group after treatment were significantly lower than those of control group. This means that CRRT therapy can effectively remove the inflammatory cytokines and reduce inflammation in patients with heat stroke, and the combination with Xuebijing is more effective than CRRT alone in reducing the systemic inflammatory response in patients with heat stroke.

The inflammation activation in patients with heat stroke is closely related to the abnormal secretion of various cytokines and the destruction of coagulation-anti-coagulation balance, TF, sTM, sE-selectin and other cytokines promote coagulation and can cause hypercoagulable state and affect the tissue microcirculation and blood perfusion[14,15]. TF is at the core of the initiation process.
of exogenous coagulation pathways and endogenous coagulation pathways, which can initiate coagulation process after forming complexes with coagulation factor FVIIa; TM is a transmembrane molecule on the surface of endothelial cells, which can interact with thrombin and promote each other, is massively generated during endothelial injury and microthrombosis, falls off into sTM and enters the blood circulation; sE-selectin is a soluble form of adhesion molecule E-selectin, which promotes platelets to aggregate in local area and form thrombus. In the study, analysis of the changes in serum levels of coagulation-related cytokines before and after treatment showed that serum TF, sTM and sE-selectin levels of both groups significantly decreased after treatment, and serum TF, sTM and sE-selectin levels of Xuebijing group after treatment were significantly lower than those of control group. This shows that CRRT can effectively inhibit the coagulation process and relieve the hypercoagulable state in patients with heat stroke; combined use of Xuebijing is more effective than CRRT alone in improving the hypercoagulable state in patients with heat stroke so as to improve the tissue microcirculation and reduce tissue damage.

Multiple organ failure is one of the most serious complications of heat stroke, which can significantly increase the mortality of the disease. Kidney is the mostly commonly involved target organ of multiple organ failure in patients with heat stroke, and when kidney damage or failure occurs, a variety of metabolites in the body can’t be discharged in time and accumulate in the body[16]. Cr and BUN are the protein metabolites in the body and excreted through the kidneys; β 2-MG and Cys-C are small molecular substances excreted by the kidney, which are re-absorbed and degraded by renal tubules after the glomerular filtration. In order to define the effects of Xuebijing combined with CRRT on renal function in patients with heat stroke, the change in serum levels of above renal function indexes were analyzed in the study before and after treatment, and the results show that serum BUN, Scr, β 2-MG and Cys-C levels of both groups significantly decreased after treatment, and serum BUN, Scr, β 2-MG and Cys-C levels of Xuebijing group after treatment were significantly lower than those of control group. This indicates that CRRT can effectively eliminate the metabolites and improve renal function in patients with heat stroke; combined use of Xuebijing is more effective than CRRT alone in improving the renal function.

The effect of Xuebijing combined with early CRRT therapy on the systemic inflammatory response and renal impairment in patients with heat stroke was mainly analyzed in the study, and the preliminary conclusions are as follows: Xuebijing combined with early CRRT therapy can significantly reduce the degree of systemic inflammatory response and the degree of renal impairment in patients with heat stroke.

References