Effects of Changtuoning and Xuebijing combined with hemoperfusion on serum inflammatory factors and myocardial enzymes in patients with acute severe organophosphorus poisoning

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ABSTRACT

Objective: To investigate the effects of Changtuoning and Xuebijing combined with hemoperfusion on serum inflammatory factors and myocardial enzymes in patients with acute severe organophosphorus pesticide poisoning (AOPP). Methods: A total of 92 patients with acute severe AOPP who were admitted to our hospital from July 2015 to June 2018 were enrolled. All patients were divided into the observation group and the control group by randomized block method (n=46). The control group was treated with Changtuoning and Xuebijing, and the observation group was treated with Changtuoning and Xuebijing combined with blood perfusion. The clinical indexes, serum inflammatory factors, myocardial enzyme indexes, complications and adverse reactions were compared between the two groups. Results: The doses of atropine, recovery waking time, ChE recovery time and hospital stay in the observation group were significantly lower than those in the control group. The cure rate in the observation group was significantly higher than that in the control group (P<0.05). There was no significant difference between the two groups (P>0.05). The levels of TNF-α, IL-8 and IL-18 in the observation group were significantly lower than those in the control group (P<0.05). The levels of CK, CK-MB, LDH and AST in the observation group were significantly lower than those in the control group (P<0.05). The incidence of adverse reactions (myalgia, fatigue, digestive tract reaction, abnormal liver function) in the observation group was significantly lower than that in the control group (P<0.05). Conclusion: Changtuoning and Xuebijing combined with hemoperfusion have significant effects on patients with acute severe organophosphorus poisoning, which can effectively reduce inflammatory factors and improve myocardial enzyme index.

1. Introduction

Acute organic phosphorus poisoning (AOPP) is one of the most common acute poisonings in the clinic, which has the characteristics of rapid onset, rapid progression of disease, high mortality and so on[1]. At present, the enteritis drug for clinical treatment of AOPP is pyraloxime iodide, which can effectively alleviate the symptoms of poisoning. However, if it is administered in large doses, it will aggravate the burden of liver and kidney in patients, which will bring difficulties to treatment. Changtuoning is essentially penehyclidine hydrochloride, a new type of anticholinergic drug with the advantages of long half-life, long duration of action, strong anticholinergic effect, etc[2,3]. Xuebijing injection is a kind of Chinese patent medicine, which can dissolve stasis and detoxify. It is often used in the treatment of multiple organ failure, sepsis, systemic inflammatory response syndrome and so on[4]. Blood perfusion is used for AOPP, which can effectively remove free organophosphorus and protein-binding toxins[5]. The effect of Changtuoning and Xuebijing combined with hemoperfusion on serum inflammatory factors and immune function in patients with acute severe AOPP was studied. The results are reported below.

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2. Materials and methods

2.1 General information

The subjects were selected from 92 patients with acute severe AOPP who were admitted to our hospital from July 2015 to June 2018. Inclusion criteria: all oral pesticide poisoning; according with the diagnostic criteria for acute severe AOPP[6]; Patients with typical muscarinic and choline-like poisoning, accompanied by coma, convulsions, pulmonary edema, respiratory failure and other symptoms; cholinesterase activity (h-CHE) < 30%; the study was approved by the ethics committee; the patient's family signed an informed consent form. Exclusion criteria: severe heart, liver and kidney dysfunction; other drug poisoning. All patients were divided into the observation group and the control group by random grouping (n=46). Among them, there were 25 males and 21 females, aged from 18 to 66 years old, with an average of (44.12±2.38) years old, and the onset time ranged from 30 min to 17 h, with an average of (5.21±2.71) h. Pesticide types: 20 cases of methamidophos, 12 cases of dichlorvos, 8 cases of dimethoate, 6 cases of parathion. There were 26 males and 20 females in the control group, aged from 17 to 67 years old, with an average of (43.68±2.79) years old. The onset time ranged from 33 minutes to 17 h, with an average of (5.06±2.85) h. Pesticide types: 19 cases of methamidophos, 11 cases of dichlorvos, 9 cases of dimethoate, 7 cases of parathion. There were no significant differences in gender, age, onset time, and poisoning pesticides between the two groups, which were comparable (P>0.05).

2.2 Treatment methods

The patients were treated routinely after admission, such as gastric lavage, diuresis, diarrhea, maintenance of water and electrolytes, and acid-base balance. Mechanical ventilation was performed on those with dyspnea. The patients in the control group were treated with Changtuoning (Chengdu Lisite Pharmaceutical Co., Ltd., National Pharmaceutical Standard H20020606) and Xuebijing (Tianjin Hongri Pharmaceutical Co., Ltd., National Pharmaceutical Standard Z20040033). Intramuscular injection of Changtuoning at the first dose was 2-4 mg, and the subsequent dose was 1-2 mg with the dosing interval of 4-6 h. The maintenance treatment was performed until the symptoms of poisoning disappeared. 100 mL of Xuebijing (manufacturer: Tianjin Hongri Pharmaceutical Co., Ltd.; National Pharmaceutical Standard: Z20040033) was added to 100 mL of normal saline with intravenous drip, 2 times/d, for 7 d. The patients in the observation group were given blood perfusion on the basis of the control group. The specific method was as follows: Resin blood perfusion device (HA330, Zhujiang Lizhu Medical Biomaterial Co., Ltd.) and Japan Kuraray KM8800 plasma switch were selected. The first dose of 4 000 U heparin was given and supplemented with 1 000 U/h. The total dose was 6 000-8 000 U, the blood flow was 200 mL/min, the perfusion time was 2 h, and the perfusion time was once every 12 h. Both two groups were treated continuously until symptoms disappeared and ChE activity recovered.

2.3 Observation indicators

(1) Clinical indicators: During the entire treatment period, the doses of atropine, recovery waking time, ChE recovery time, hospitalization time, mortality and cure rate were recorded in the two groups; (2) Serum inflammatory factors: Before and after treatment, fasting venous blood samples of 4 mL in the morning were collected and centrifuged for 15 min at 3 000 r/min. Serum samples were separated and stored at – 80 °C for examination. Tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8) and interleukin-18 (IL-18) were detected by enzyme-linked immunosorbent assay. The kits were purchased from Shanghai Kanglang Biotechnology Co., Ltd; (3) Cardiac enzymes: Creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) were detected by colorimetry, and creatine kinase isoenzyme (CK-MB) was detected by immunosuppressive method. The kits were purchased from Nanjing Jiancheng Institute of Bioengineering. The detection equipment was Spectra Max M3 multi-functional enzyme label instrument of MD Company of the United States; (4) Incidence of complications: Complications of the two groups were recorded in the course of treatment, such as intermediate syndrome, respiratory failure, pulmonary infection, pulmonary edema and gastrointestinal bleeding; (5) The occurrence of adverse reactions: The occurrence of adverse reactions of two groups of patients in the course of treatment were recorded.

2.4 Statistical analysis

SPSS 19.0 software was used to analyze and process the results of the study. The dose of atropine, recovery waking time, ChE recovery time, hospitalization time, serum inflammatory factor, myocardial enzyme index were measurement data, which were analyzed by t test method. The cure rate, mortality rate, complications, and adverse reactions were count data, which were analyzed by test methods. When P<0.05, the difference was statistically significant.

3. Results

3.1 Comparison of clinical indicators between the two groups of patients

The doses of atropine, recovery waking time, ChE recovery time and hospital stay in the observation group were significantly lower than those in the control group. The cure rate of the observation group was significantly higher than that of the control group (P<0.05). There was no significant difference between the two groups (P>0.05). The results were shown in Table 1.
3.2 Comparison of serum inflammatory factors between the two groups

There was no significant difference in the levels of serum inflammatory factors between the two groups before treatment ($P>0.05$). After treatment, the levels of serum inflammatory factors were lower than those before treatment ($P<0.05$), and TNF-$\alpha$, IL-8 and IL-18 in the observation group were significantly lower than those in the control group ($P<0.05$). The results were shown in table 2.

3.3 Comparison of myocardial enzymes in two groups of patients

There was no significant difference in myocardial enzyme index between the two groups before treatment ($P>0.05$). The myocardial enzyme index of the two groups after treatment was lower than those before treatment ($P<0.05$), and levels of CK, CK-MB, LDH, AST of the observation group were significantly lower than those of the control group ($P<0.05$). The results were shown in Table 3.

3.4 Comparison of complications in two groups of patients

The incidence of each complication (intermediate syndrome, respiratory failure, pulmonary infection, pulmonary edema) in the observation group were significantly lower than those in the control group ($P<0.05$). The results were shown in Table 4.

3.5 Comparison of the incidence of adverse reactions in the two groups

The incidence of adverse reactions (myalgia, fatigue, digestive tract reaction, abnormal liver function) in the observation group

### Table 1.
Comparison of clinical indicators between the two groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Atropine dose (mg)</th>
<th>Recovery waking time (h)</th>
<th>ChE recovery time (d)</th>
<th>Hospital stay (d)</th>
<th>Cure rate (%)</th>
<th>Mortality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation</td>
<td>46</td>
<td>123.69±15.37</td>
<td>11.26±4.17</td>
<td>7.53±2.94</td>
<td>10.28±3.65</td>
<td>43(93.5)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>The control group</td>
<td>46</td>
<td>176.48±18.51</td>
<td>16.81±4.63</td>
<td>13.27±4.12</td>
<td>17.49±4.77</td>
<td>35(76.1)</td>
<td>3(6.5)</td>
</tr>
</tbody>
</table>

### Table 2.
Comparison of serum inflammatory factors between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>TNF-$\alpha$ (ng/L)</th>
<th>IL-8(ng/L)</th>
<th>IL-18(ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation</td>
<td>Prior treatment</td>
<td>5.24±1.05$^a$</td>
<td>51.33±9.82$^a$</td>
<td>91.26±12.57$^a$</td>
</tr>
<tr>
<td></td>
<td>Post treatment</td>
<td>2.36±0.91$^bc$</td>
<td>17.29±5.26$^bc$</td>
<td>58.35±10.34$^bc$</td>
</tr>
<tr>
<td>The control group</td>
<td>Prior treatment</td>
<td>5.41±1.02</td>
<td>52.04±9.43</td>
<td>91.48±13.49</td>
</tr>
<tr>
<td></td>
<td>Post treatment</td>
<td>3.97±0.96</td>
<td>29.05±7.31</td>
<td>76.48±10.55</td>
</tr>
</tbody>
</table>

Note: comparison between groups before treatment, $P>0.05$; Intra-group comparison before and after treatment, $P<0.05$; comparison between groups after treatment, $P<0.05$.

### Table 3.
Comparison of myocardial enzymes between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>CK (U/L)</th>
<th>CK-MB (U/L)</th>
<th>LDH (U/L)</th>
<th>AST (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation</td>
<td>Pre treatment</td>
<td>227.19±91.23$^a$</td>
<td>68.64±12.39$^a$</td>
<td>425.37±32.51$^a$</td>
<td>92.31±12.72$^a$</td>
</tr>
<tr>
<td></td>
<td>Post treatment</td>
<td>107.48±21.46$^bc$</td>
<td>31.17±4.15$^bc$</td>
<td>217.19±21.36$^bc$</td>
<td>27.49±5.28$^bc$</td>
</tr>
<tr>
<td>The control group</td>
<td>Pre treatment</td>
<td>221.39±88.54</td>
<td>65.25±10.27</td>
<td>430.61±30.81</td>
<td>90.67±11.42</td>
</tr>
<tr>
<td></td>
<td>Post treatment</td>
<td>131.05±20.31$^b$</td>
<td>42.51±4.48$^b$</td>
<td>305.47±27.59$^b$</td>
<td>70.51±8.73$^b$</td>
</tr>
</tbody>
</table>

Note: comparison between groups before treatment, $P>0.05$; Intra-group comparison before and after treatment, $P<0.05$; comparison between groups after treatment, $P<0.05$.

### Table 4.
Comparison of complications in two groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>intermediate syndrome</th>
<th>respiratory failure</th>
<th>pulmonary infection</th>
<th>pulmonary edema</th>
<th>Gastrointestinal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation</td>
<td>46</td>
<td>19(41.3)</td>
<td>13(28.3)</td>
<td>16(34.8)</td>
<td>15(32.6)</td>
<td>4(8.7)</td>
</tr>
<tr>
<td>The control group</td>
<td>46</td>
<td>31(67.4)</td>
<td>25(54.3)</td>
<td>30(65.2)</td>
<td>26(56.5)</td>
<td>3(6.5)</td>
</tr>
</tbody>
</table>

Note: comparison between groups before treatment, $P>0.05$; Intra-group comparison before and after treatment, $P<0.05$; comparison between groups after treatment, $P<0.05$.
was significantly lower than that in the control group ($P<0.05$). The results were shown in Table 5.

### 4. Discussion

Severe AOPP is a common critical disease. Its pathogenesis is the combination of organic phosphorus and cholinesterase (ChE) to form phosphorylesterase, which leads to the inactivation of ChE and causes acetylcholine to accumulate in the synaptic cleft, causing the nerve muscle transmission to impede and damage to the body’s nervous system[7,8]. Hemoperfusion is a common method for the treatment of severe AOPP. By means of extracorporeal circulation device and adsorbent, the pathogenic substances in the blood of patients can be removed, thus producing the effect of blood purification. Hemoperfusion is the best method for AOPP patients in the first 6-8 h[9,10].

Changtuoning has specific anti-Peripheral and central nervous system M and N choline receptors, which can effectively alleviate muscarinic, nicotinic and central nervous system poisoning. It is highly selective to M receptors and selectively acts on M1 and M3 receptors, while it has little effect on the M2 receptor and therefore has no effect on heart rate[11,12]. Changtuoning has good lipid solubility, can penetrate the blood-brain barrier, and inhibit the agonistic effect of acetylcholine on M and N receptors in the brain, and effectively alleviate clinical symptoms such as coma, convulsions and weakness caused by poisoning[13,14].

Xuebijing injection is a kind of traditional Chinese medicine compound preparation. Its main components are safflower, red peony, Ligusticum wallichii, Salvia miltiorrhiza and angelica. It has the functions of nourishing blood gas and dredging collaterals. It can be used to treat sepsis, acute pancreatitis, systemic inflammatory response syndrome and other acute and severe diseases[15]. Tian Yinghai et al. had shown[16] that Xuebijing injection in the treatment of severe AOPP patients can effectively inhibit inflammation, reduce complications, shorten the course of disease, and improve clinical efficacy.

The results of this study showed that the doses of atropine, recovery waking time, ChE recovery time, hospitalization time and mortality in the observation group were significantly lower than those in the control group, and the cure rate in the observation group was significantly higher than that in the control group ($P<0.05$). It showed that Changtuoning and Xuebijing combined with blood perfusion therapy had significant curative effect on severe AOPP, which quickly promoted the recovery of patients, reduced the dosage of drugs and shortened the length of hospital stay.

When acute poisoning occurs, it can activate the inflammatory reaction in the body, stimulate the inflammation-related cells to secrete a large amount of inflammatory mediators, causing a waterfall-like inflammatory reaction[17]. TNF-$\alpha$ is an important pro-inflammatory factor in the body, which can promote the production, aggregation and adhesion of inflammatory cells, and further amplify the inflammatory response and accelerate the inflammatory damage of tissue cells[18,19]. IL-8 activates neutrophils, causes respiratory burst reactions, produces a large number of toxic secondary metabolites, causes cell death, leads to vascular endothelial damage, activates coagulation and fibrinolysis system, leads to increased vascular permeability and microthrombus formation, aggravating microcirculatory disorders, eventually causing multiple organ dysfunction[20]. IL-18 is also an important pro-inflammatory factor that activates mononuclear macrophages, promotes the secretion of various inflammatory factors and adhesion molecules, and aggravates the body’s inflammatory response[21]. In the results of this study, the levels of TNF-$\alpha$, IL-8, and IL-18 of the observation group were significantly lower than those of the control group ($P<0.05$). It showed that after combination therapy, the degree of inflammation in patients was significantly reduced, because the safflower in Xuebijing will improve the body's microcirculation, anti-oxidation, anti-inflammatory, etc. Paeonia can reduce capillary permeability and prevent NO toxicity damage. Ligusticum wallichii can inhibit neutrophil activation and inflammatory cell aggregation, and improve vascular endothelial function. Salvia miltiorrhiza can inhibit platelet aggregation, resist lipid peroxidation, scavenge free radicals and improve microcirculation. Angelica sinensis can inhibit platelet aggregation and improve immunity. Therefore, Xuebijing can produce better inhibition of inflammatory response through various ways. The blood perfusion directly removes the toxins produced in the body through purification, preventing damage caused by the accumulation of toxins in the body.

When AOPP occurs, the deposition of a large amount of acetylcholine can cause calcium overload in myocardial cells, leading to myocardial degeneration, necrosis, myocardial fiber breakage, and striated muscle lysis. It can seriously impair myocardial function, and in severe cases it can cause heart failure, arrhythmia and so on[22]. Myocardial zymogram can effectively reflect the degree of myocardial damage. The results of this study showed that the levels of CK, CK-MB, LDH and AST in the observation group were significantly lower than those in the control group ($P<0.05$). It shows that after combined treatment, the patient’s myocardial function is effectively protected and improved, preventing serious
complications in patients. Because Changtuoning can reduce the resistance of peripheral blood vessels and pre-cardiac load, and a variety of traditional Chinese medicine ingredients in Xuebijing can prevent myocardial damage caused by insufficient oxygen supply or blood gas, and improve the function of damaged cardiomyocytes. At the same time, it can resist lipid peroxidation, scavenge free radicals, and combine blood perfusion. With the circulation device, it can not only effectively remove toxins, but also promote blood circulation of the body, thereby effectively reducing myocardial enzyme levels, protecting myocardial function and improving cardiac function.

The results of this study also show that the incidence of complications and adverse reactions in the observation group are significantly lower than that of the control group (P<0.05). It is suggested that the combination of the three has a significant effect on patients with severe AOPP, effectively eliminating the exogenous and endogenous toxins of the body. At the same time, it improves the blood circulation of the body, inhibits platelet aggregation, scavenge free radicals, reduces the degree of inflammation, effectively protects the functions of various organs, reduces the occurrence of various complications, which is safe and reliable, reducing the occurrence of adverse reactions.

In summary, Changtuoning and Xuebijing combined with hemoperfusion have significant effects on patients with severe AOPP, which can effectively reduce inflammatory factors and improve myocardial enzyme index.

References