Effect of alprostadil combined with butylphthalide on the serum inflammatory factors and coagulable function in patients with acute ischemic stroke

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Objective: To observe the effect of alprostadil combined with butylphthalide on the serum inflammatory factors, coagulable function in patients of acute ischemic stroke. Methods: A total of 84 cases of patients with acute ischemic stroke were randomly divided into observation group (44 cases) and control group (40 cases). The observation group was given alprostadil combined and butylphthalide based on conventional treatment, and the control group was given alprostadil based on conventional treatment. Treatment was developed for 14 d to observe the changes of serum inflammatory factors (IL-6, IL-8, CRP, TNF-α) and coagulation correlated parameters (PT, FIB, DDI, TXB2, PAI-1) between the two groups. Results: After treatment, IL-6, IL-8, CRP, TNF-α of the two groups decreased obviously compared with before, PT increased and FIB, DDI, TXB2, PAI-1 decreased obviously compared with before. All indexes of the observation group were improved more significantly than that of the control group, with statistical difference. Conclusion: Alprostadil combined with butylphthalide can help to inhibit inflammatory reaction and improve high coagulation state in treatment of acute ischemic stroke.

1. Introduction

Acute ischemic stroke is a common clinical disease and has a high morbidity and mortality. Effective intervention on various pathological links after onset improves prognosis of patients[1]. Protecting brain cells on acute period of stroke and promoting the function of the nerve remain important goals of therapy. Obviously, improving the function of blood coagulation and inhibiting the inflammatory response are beneficial to achieve the above purposes[2]. Alprostadil and butylphthalide are commonly used drugs for the treatment of acute ischemic stroke. The advantages of the combined use of these two drugs in clinical have not yet fully understood even though it is widely applied in recent years. The effect of alprostadil combined with butylphthalide on the serum inflammatory factors and coagulable function was investigated to provide reference for clinical practice. Presently reports as follows.

2. Clinical data and methods

2.1 General data

From February 2013 to October 2015, patients of acute ischemic stroke from our departments were selected with first onset and being hospitalized within 72 hours after the onset, and diagnosed by cranioencebral CT or MRI according to the diagnostic criteria formulated by The Neurology branch of Chinese medical association in 2010[3]. Exclusion criteria: rule out with severe heart,
liver, kidney, lung, hematopoietic system, endocrine system disease and tumor patients; exclusion of cerebral hemorrhage, herniation of brain, deep coma and uncontrolled acute infection, for patients with a tendency of spontaneous bleeding; patients who were allergic to drugs used in this study; patients who did not signed informed consent. A total of 84 cases of patients were selected and randomly divided into control group and observation group. In the observation group, total of 44 cases were composed of 26 male and 18 female, who were 45-77 (60.25±13.75) years old; the time of onset to be hospitalized were 3-26 (6.42±1.64) h; complication: 21 cases of hypertension and 15 cases of diabetes. In the control group, total of 40 cases were composed of 23 male and 17 female, who were 46-78 (62.67±14.53) years old; the time of onset to be hospitalized were 3-30 (6.50±1.37) h; complication: 20 cases of hypertension and 13 cases of diabetes. The gender, age, the time of onset to be hospitalized and complication of the two groups were not statistically different (P>0.05).

2.2 Therapeutic method

Conventional therapy was adopted after cases were selected, such as platelet aggregation, oxygen, control of intracranial pressure, protecting the functions of brain cells and nerve, maintaining electrolyte disturbances and so on. Make the blood pressure of hypertension and blood sugar of diabetes standards.

In the observation group, alprostadil (Manufacturer: Beijing Taide pharmaceutical co., LTD., approved by the H10980024) and butylphthalide (Manufacturer: CSPC NBP pharmaceutical co., LTD., approved by the H200050299) were additionally provided on the basis of above therapy. Specifically, 10 μg of alprostadil were added to 10 mL of physiological saline and received intravenous injections once a day, 0.2 g of oral butylphthalide capsule was taken three times a day. Combination therapy was adopted for 14 d.

In the control group, alprostadil was additionally provided on the basis of above therapy and continuously for 14 d, the method was same with observation group.

2.3 Observational index

Inflammatory factors include interleukin-6 (IL-6), interleukin-8 (IL-8), C-reactive protein (CRP) and tumor necrosis factor (TNF-α). Enzyme-linked immunosorbent assay was adopted to detect IL-6, IL-8 and TNF-α, the kits were manufactured by Beijing Jingmei biotechnology CO., LTD. Immunoturbidimetry was adopted to detect CRP, the kits were manufactured by RANDOX company. Coagulative function indexes include prothrombin time (PT), D-dimer (DDI), fibrinogen (FIB), thromboxane B2 (TXB2). PT/s, DDI and FIB were detected by PUN-2048A coagulometer, TXB2 and PAI-1 were detected by enzyme-linked immunosorbent assay, and the kits were made in Shanghai Yadu biotechnology research institute.

2.4 Statistics

SPSS 17.0 statistical software was adopted for data analysis. Measurement data was carried out by t test and described as mean ± standard deviation. Values of P<0.05 were considered to be statistically significant.

3. Results

3.1 Comparison of the levels of inflammatory factors before and after treatment

Levels of IL-6, IL-8, CRP and TNF-α in both groups were not statistically significant before treatment (P>0.05). While the levels of IL-6, IL-8, CRP and TNF-α in both groups significantly decreased after treatment (P<0.05). The levels of IL-6, IL-8, CRP and TNF-α in the observation group were measured with (27.72±8.34) ng/L, (146.70±48.42) pg/mL, (8.12±2.54) mg/L, (1.78±0.21) μg/L after treatment, respectively, which were lower than that of the control group and considered to be statistically significant (P<0.05). See Table 1.

3.2 Comparison of the levels of coagulative function indexes before and after treatment

Levels of PT, FIB, DDI, TXB2 and PAI-1 in both groups were not statistically significant before treatment (P>0.05). The levels of PT, FIB, DDI, TXB2 and PAI-1 in both groups significantly decreased after treatment (P<0.05). The levels of PT, FIB, DDI, TXB2 and PAI-1 in both groups significantly increased (P<0.05), while the level of PT in both groups significantly increased

<table>
<thead>
<tr>
<th>Group</th>
<th>Time point</th>
<th>IL-6 (ng/mL)</th>
<th>IL-8 (pg/mL)</th>
<th>CRP (mg/L)</th>
<th>TNF-α (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>Before treatment</td>
<td>64.56±16.75</td>
<td>458.64±74.33</td>
<td>31.62±11.25</td>
<td>3.06±0.75</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>27.72±8.34</td>
<td>146.70±48.42</td>
<td>8.12±2.54</td>
<td>1.78±0.21</td>
</tr>
<tr>
<td>Control</td>
<td>Before treatment</td>
<td>66.32±18.58</td>
<td>464.48±78.84</td>
<td>32.17±12.74</td>
<td>2.05±0.69</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>41.60±9.65</td>
<td>190.37±56.29</td>
<td>15.73±4.32</td>
<td>2.05±0.26</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, △P<0.05; compared with observation group after treatment, ▲P<0.05
after treatment ($P<0.05$). The levels of PT, FIB, DDI, TXB$_2$ and PAI-1 in the observation group were measured with (14.31±1.10) s, (3.17±0.63) g/L, (0.53±0.24) μg/mL, (63.57±5.57) pg/mL, (8.31±1.15) ng/mL after treatment, respectively, whose variation is greater than the control group and considered to be statistically significant ($P<0.05$). See Table 2.

### Table 2

Comparison of the levels of coagulative function indexes before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Time point</th>
<th>PT (s)</th>
<th>FIB (g/L)</th>
<th>DDI (μg/mL)</th>
<th>TXB$_2$ (pg/mL)</th>
<th>PAI-1 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>Before treatment</td>
<td>9.36±1.42</td>
<td>4.43±1.27</td>
<td>1.12±0.65</td>
<td>135.93±18.77</td>
<td>13.71±3.31</td>
</tr>
<tr>
<td>Control</td>
<td>Before treatment</td>
<td>14.31±1.10</td>
<td>3.17±0.63</td>
<td>0.53±0.24</td>
<td>63.57±5.57</td>
<td>8.31±1.15</td>
</tr>
<tr>
<td>(44 cases)</td>
<td>After treatment</td>
<td>11.50±1.25</td>
<td>3.72±0.72</td>
<td>0.85±0.34</td>
<td>132.87±19.82</td>
<td>13.44±3.37</td>
</tr>
<tr>
<td>(40 cases)</td>
<td>After treatment</td>
<td>11.44±1.37</td>
<td>4.49±1.35</td>
<td>1.16±0.74</td>
<td>82.32±0.61</td>
<td>11.44±2.29</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, △$P<0.05$; compared with observation group after treatment, ▲$P<0.05$

### 4. Discussion

Thrombus is easily caused in hypercoagulable state and leads to acute ischemic stroke. It persists for a long time after onset[4], may induce new thrombus formation and make the illness even worse. Early thrombolytic is the key to successful treatment for the patients, but majority of patients are unable to receive thrombolytic treatment limited by the short window time[5]. Positive interventions should be carried out to improve the prognosis of patients in the follow-up pathological links in the development of this disease. Improving hypercoagulable state to prevent thrombosis, reducing the damage to nerve cells and promoting their functional recovery are important parts of the treatment[6,7]. Alprostadil and butylphthalide used in this study are commonly applied for these key links in recent years. It has reported that the combined use of these two drugs could increase curative effect, but such reports hadn’t been seen so much.

The effect of alprostadil combined with butylphthalide on the serum inflammatory factors and coagulable function in patients of acute ischemic stroke was investigated in this study. Suppression of inflammation aims to reduce the nerve cell damage, brain anoxia and subsequent encephalema after thrombogenesis both could stimulate the expansion of oxidative stress reaction[8,9], and improve the synthesis and secretion of inflammatory factors. It was reported that significantly systemic inflammatory reaction could damage the body, especially the nerve cells, and result in worse illness and poor prognosis[6]. Improving coagulation function to alleviate hypercoagulable state not only could prevent thrombus, but also promote the blood rheology to improve and reduce cerebral ischemic injury[10]. Alprostadil was applied in clinical for a long time. Prostaglandin E1 is wrapped by lipid microspheres and selective gathered at the lesion site and local vessel expansion[11]. The inhibition of thromboxane A$_2$ release can improve hypoxia and ischemia state, and promote the establishment of the microcirculation[12]. Anti-fibrosis and antagonism of calcium influx could suppress oxidative stress and ischemia-reperfusion injury. It is also reported that this drug could significantly inhibit platelet aggregation, expand cerebrovascular, improve the local blood circulation and contribute to inhibit oxidative stress[10,12]. Butylphthalide is a new drug in clinical, whose active ingredient is racemization-3-n-butylbenzene, it could inhibit brain ischemic injury, such as effectively regulate on arachidonic acid and inhibition of platelet aggregation[13]. It acts on the brain mitochondria and promotes mitochondrial membrane fluidity, quickly recovers the blood supply on ischemia area of embolization, protects the mitochondria structure and function to reduce the nerve cell damage[14]. It also refactors local blood circulation and promotes the establishment of collateral circulation, improves tolerance of hypoxia and lack of sugar to reduce the apoptosis[15]. It inhibits the synthesis and release of glutamate, and inhibits oxidative stress to reduce the generation of inflammation factors[16]. Therefore, alprostadil combined with butylphthalide has cooperating function on pharmacological mechanism, which was confirmed in this study. IL-6, IL-8, CRP and TNF-α are inflammatory factors which were often detected in clinical and investigated in this study, they are all proinflammatory factors, could reflect the strength of the oxidative stress and significantly increase in acute ischemic stroke[17–20]. PT, FIB, DDI, TXB$_2$ and PAI-1 are all common coagulative function indexes, could well reflect the body’s blood coagulation state, and are abnormal in thrombotic diseases[7]. The results indicated that the indexes of inflammatory factors and blood coagulation function in the observation group after treatment were better than that in the control group. Lower level of inflammatory factors means lower oxidative stress intensity and less inflammatory damage to nerve cells of patients. The indexes of blood coagulation function improved significantly meant high blood coagulation state improved better, and was benefit to prevent thrombosis and improve brain ischemia and hypoxia. In fact, there is a close relationship between inflammatory reaction intensity and hypercoagulable state, and an impact on each other exists on the improvement of both. But for all that, the improvement of the two kinds of indexes both benefits the patients. Some studies have showed that the improvement of nerve function under alprostadil combined with butylphthalide was better than use one of them[15].
In conclusion, alprostadil combined with butylphthalide can better help to inhibit inflammatory reaction and improve high coagulation state in treatment of acute ischemic stroke, and better to improve prognosis.

References


