Effect of adjuvant argatroban therapy on neurological function, endothelial injury and inflammation state in patient with acute cerebral infarction

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Objective: To analyze the effect of adjuvant argatroban therapy on neurological function, endothelial injury and inflammation state in patient with acute cerebral infarction. Methods: A total of 118 patients with acute cerebral infarction were divided into observation group and control group according to the random number table, control group received conventional treatment, observation group received argatroban + conventional treatment, and then differences in TCD cerebral blood flow, serum neurological function, endothelial injury and inflammatory marker levels were compared between two groups after treatment. Results: TCD MCA and ACA values of observation group after treatment were higher than those of control group ($P<0.05$); serum neurological function indexes copeptin, NT-proBNP, PAO and S-100B levels of observation group after treatment were lower than those of control group, endothelial injury index ET-1 level was lower than that of control group, NO and CGRP levels were higher than those of control group, and inflammatory markers hs-CRP, TNF-$\alpha$, IL-6, MMP-9 and Lp-PLA2 levels were lower than those of control group ($P<0.05$). Conclusions: Adjuvant argatroban therapy can optimize the overall condition in patients with acute cerebral infarction, and plays a positive role in improving the neurological function, reducing endothelial injury and inflammation state, etc.

1. Introduction

Acute cerebral infarction (ACI) trends to occur in middle-aged and old people and the latest research on the mechanism of ACI shows that both endothelial injury and systemic inflammation state are independent risk factors leading to the disease. There are many clinical studies on the treatment of ACI, but the overall effect has certain limitations [1,2]. Argatroban is a new anticoagulant drug that reversibly combines thrombin to make it deactivated and thus exerts anticoagulation effect. Compared with common anticoagulant drugs such as heparin, argatroban has highly selective effect on direct anticoagulants, has strong anticoagulant effect and causes little damage to other systems, so it has received the attention from many clinical researchers [3]. In the study, adjuvant argatroban therapy was applied in ACI patients, the changes of neural function in patients were observed, and meanwhile, the effect of argatroban on endothelial injury and inflammatory state was mainly stated.

2. Materials and methods

2.1. General information

A total of 118 patients with acute cerebral infarction treated in our hospital from August 2012 to August 2015 were included in the study. Inclusion criteria were as follows: 1) in accordance with the diagnostic criteria for acute cerebral infarction established by the WHO; 2) did not receive major surgery within 6 months; 3) patients’ families signed informed consent; 4) the data was complete. Exclusion criteria: (1) with liver and kidney dysfunction; 2) with long-term use of anticoagulant drugs; 3) with argatroban allergies;
with malignant tumor diseases.

All 118 cases of patients met the above research criteria and were divided into observation group and control group \((n=59)\) according to the random number table. Control group included 31 male cases and 28 female cases, they were 42-71 years old, the average age was \((59.82\pm7.11)\) years, the course of disease was 3-21 h and the average course was \((11.29\pm3.24)\) h; observation group included 30 male cases and 29 female cases, they were 44-70 years old, the average age was \((60.76\pm7.09)\) years, the course of disease was 4-24 h and the average course was \((11.87\pm3.52)\) h. The two groups showed no statistically difference in gender, age and disease time \((P>0.05)\) and could receive subsequent treatment.

2.2. Treatment methods

The control group received conventional treatment for acute cerebral infarction: oral administration of aspirin enteric-coated tablets at night, 0.1 g/time, 1 time a day; intravenous drip of the solution of edaravone injection 30 mg and 250 mL saline, 2 times a day; intravenous drip of the solution of salvia ligustrazin injection 10 mL and 5% glucose injection 250 mL, 1 time a day; atorvastatin taken after dinner, 10 mg/time, 1 time a day.

Observation group received conventional treatment + argatroban, specifically as follows: argatroban injection 60 mg in 500 mL saline, infused by infusion pump in 24 h, on d1 and d2. Argatroban injection 10 mg in 100 mL saline, infused by infusion pump within 3 h, 2 times/d, on d3, d4 and d5. Argatroban injection 10 mg in 100 mL saline, infused by infusion pump within 3 h, 1 time/d, on d6-d10. Conventional treatment was the same as that of control group.

2.3. Cerebral blood flow detection by transcranial Doppler (TCD)

Before treatment and 1 month after treatment, TCD was used to detect cerebral blood flow state in patients, and the mean blood flow velocity \((V_m)\) of middle cerebral artery (MCA) and anterior cerebral artery (ACA) was detected.

2.4. Serum indexes

One week after treatment, 5ml of fasting peripheral venous blood was extracted from patients and centrifuged at room temperature and low speed, and then supernatant was collected and cryopreserved at -70 °C for detection. 1) Neurological function: copeptin, N-terminal pro-brain natriuretic peptide (NT-proBNP), polyamine oxidase (PAO) and S-100B protein (S-100B). 2) Endothelial injury: nitrate reductase was used to determine nitric oxide (NO) level, and RIA method was used to determine endothelin-1 (ET-1) and calcitonin gene-related peptide (CGRP) levels. 3) Inflammatory markers: double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) was used to detect hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-α \((TNF-\alpha)\), interleukin-6 (IL-6), matrix metalloproteinase (MMP-9) and lipoprotein-associated phospholipase (Lp-PLA2).

2.5. Statistical methods

Obtained data was input in SPSS21.0 for analysis and processing, measurement data was in terms of average ± standard deviation, comparison between two groups was performed by \(t\) test, and \(P<0.05\) was the standard of statistical significant differences.

3. Results

3.1. Cerebral blood flow

Differences in MCA and ACA values of two groups were not statistically significant \((P>0.05)\), MCA and ACA values of both groups after treatment were higher than those before treatment and the increasing trend of observation group was more significant \((P<0.05)\), and the MCA and ACA values of observation group after treatment were higher than those of control group \((P<0.05)\), shown in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Case No.</th>
<th>MCA Before treatment</th>
<th>MCA After treatment</th>
<th>ACA Before treatment</th>
<th>ACA After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>59</td>
<td>42.17±4.95</td>
<td>53.76±6.12</td>
<td>36.27±4.09</td>
<td>47.62±5.38</td>
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<tr>
<td>Control group</td>
<td>59</td>
<td>43.25±4.78</td>
<td>48.31±5.28</td>
<td>35.92±4.13</td>
<td>41.95±4.85</td>
</tr>
<tr>
<td>(t)</td>
<td></td>
<td>0.217</td>
<td>6.293</td>
<td>0.189</td>
<td>7.283</td>
</tr>
<tr>
<td>(P)</td>
<td></td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Case No.</th>
<th>Copeptin (pmol/L)</th>
<th>NT-proBNP (pmol/L)</th>
<th>PAO (U/L)</th>
<th>S-100B (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>59</td>
<td>2.17±0.29</td>
<td>105.38±13.76</td>
<td>3.84±0.47</td>
<td>0.81±0.09</td>
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<td>Control group</td>
<td>59</td>
<td>4.25±0.49</td>
<td>195.32±23.41</td>
<td>7.69±0.85</td>
<td>1.17±0.18</td>
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<tr>
<td>(t)</td>
<td></td>
<td>5.568</td>
<td>12.126</td>
<td>8.985</td>
<td>5.674</td>
</tr>
<tr>
<td>(P)</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
3.2. Neurological function indexes

Serum copeptin, NT-proBNP, PAO and S-100B levels of observation group after treatment were lower than those of control group (P<0.05), shown in Table 2.

3.3. Endothelial function indexes

Serum ET-1 level of observation group after treatment was lower than that of control group while NO and CGRP levels were higher (P<0.05), shown in Table 3.

3.4. Inflammatory markers

Serum hs-CRP, TNF-α, IL-6, MMP-9 and Lp-PLA2 levels of observation group after treatment were lower than those of control group (P<0.05), shown in Table 4.

4. Discussion

ACI is with increasing incidence year by year at present in China, and its high-risk groups are middle-aged and old people complicated with hypertension, diabetes and other independent risk factors. At present, varying degrees of limbs dysfunction is left in most patients after acute cerebral infarction attack, and meanwhile, it is associated with depression, anxiety and other negative mood, seriously damaging people’s life quality[4]. How to improve treatment effect and optimize the overall condition and treatment outcome after the onset of ACI has been the focus of the clinical study, and at present, some scholars recommend adding argatroban in the treatment of ACI. Argatroban is thrombin inhibitor, which is reversibly combined with the active site of thrombin to make it inactivated, and can reduce the circulation hypercoagulability in ACI patients and avoid secondary embolism events[5,6]. Compared with other anticoagulants, argatroban has higher selectivity, and will not affect the serine protease during the treatment; at the same time, argatroban is different from heparin and other anticoagulant drugs, does not to need the antithrombin as a cofactor, and can exert direct anticoagulation effect[7]. The many anticoagulation advantages of argatroban make it receive more and more clinical attention, it was used in the study for the treatment of ACI patients admitted in our hospital, and the effect of argatroban on neurological function, endothelial injury, inflammation status and other aspects was mainly stated.

The main clinical manifestation of patients with ACI is neurological function damage, and this is the root of poor long-term treatment effect and declined quality of life. Ultrasonic rheoencephalogram and serum neurological function-related parameters are the direct and indirect ways to reflect the neurological function, and it was found in the study that TCD MCA and ACA values of observation group after treatment were higher, and serum copeptin, NT-proBNP, PAO and S-100B levels were lower. Blood flow velocity of middle cerebral artery (MCA) and anterior cerebral artery (ACA) reflects the brain blood supply, and decreased blood flow velocity of MCA and ACA after cerebral infarction mostly indicates severe cerebral ischemia hypoxia and cerebral function damage in infarction areal[8,9]. Copeptin, NT-proBNP, PAO and S-100B are the clinical serum indexes more commonly used to indirectly reflect the brain function. Recent study has shown that increased serum levels of copeptin are highly correlated with poor prognosis of cerebrovascular diseases, which is associated with the aggravated cerebral edema caused by water-sodium retention in the body under stress[10]. NT-proBNP is BNP split product, the trend of its serum level is consistent with that of BNP, its level is the highest in brain tissue, and after ACI happens, it may pass through the blood brain barrier into the blood circulation and be detected. PAO is the rate-limiting enzyme of dopamine interchange approach in the brain, it regulates the brain dopamine levels, and animal ACI model shows that serum PAO activity increases sharply after the onset. S-100B is a small molecular calcium-binding protein, gathers in the central nervous astrocytes, and plays an important role in secondary infarction of the surrounding area and delaying neural functional recovery after infarction[11,12]. The above results indicated that after argatroban was
added in the treatment, the cerebral blood flow in patients increased and the related parameters in serum changed to the direction of cerebral functional recovery, which were basically consistent with the reported results of previous literature, and were mainly because that argatroban early recanalized the blood vessels with infarction, restored brain blood and oxygen supply in infarction area, etc.

Endothelial dysfunction and systemic inflammation state are two most important precipitating factors leading to ACI, and also the two main theories in the research of basic ACI mechanisms. NO, ET-1 and CGRP are typical endothelial function indexes, hs-CRP, TNF-α, IL-6, MMP-9, Lp-PLA2 are the inflammatory markers with more clinical report, the levels of above indexes were detected in the study in order to make clear the intervention effect of argatroban on endothelial function and of inflammatory injury in patients with ACI. Test results of endothelial function indexes showed that endothelial injury index ET-1 level of observation group after treatment was lower while NO and CGRP levels were higher. NO is the most important vasodilation factor in the body, ET-1 is the most powerful and enduring vasoconstriction substance, and study has shown that the more severe the vascular endothelial injury in patients with ACI, the higher the ET level[13]. CGRP is a newly discovered active substance with powerful vasodilation effect, and can increase both blood flow and positive inotropic action. Above results of endothelial indexes show that argatroban can promote the endothelial function recovery and inhibit the further development of endothelial dysfunction in patients with ACI. Detection results of inflammatory marker levels showed that serum hs-CRP, TNF-α, IL-6, MMP-9 and Lp-PLA2 levels of observation group decreased. hs-CRP, TNF-α and IL-6 are the typical inflammatory factors with the most clinical research, hs-CRP has high sensitivity and can be massively secreted in early inflammation, and TNF-α and IL-6 have potent proinflammatory effect and play a key role in the process of inflammatory cascade. Many clinical studies have confirmed that MMP-9 has a close relationship with the severity of ACI and prognosis of neurological function, and is closely related to the neutrophil infiltration and blood-brain barrier damage[14]. Lp-PLA2 is secreted by white blood cells, and the latest research in the United States has found that Lp-PLA2 level is independently associated with cerebral infarction and Lp-PLA2 inhibitors can reduce atherosclerosis plaque formation[15]. The above results indicate that argatroban can reduce the systemic inflammation state and promote the improvement of the overall condition in patients with ACI, but its promotion on anti-inflammatory mechanism needs to be determined by further research.

To sum up, adjuvant argatroban therapy for patients with acute cerebral infarction plays a positive role in optimizing patients’ neurological function and reducing endothelial injury and inflammation state.

References