Clinical study about mild hypothermia + intravenous thrombolysis in promoting the neural functional recovery in patients with acute cerebral infarction

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Abstract

Objective: To explore the efficacy of mild hypothermia + intravenous thrombolysis in promoting the neural functional recovery in patients with acute cerebral infarction. Methods: A total of 176 patients with acute cerebral infarction who were treated in our hospital between September 2015 and February 2017 were reviewed and divided into the routine group (n=100 cases, receiving routine intravenous thrombolysis therapy) and the mild hypothermia group (n=76, receiving mild hypothermia + intravenous thrombolysis therapy), and the treatment lasted for 1 week. The differences in serum levels of nerve injury indexes, inflammatory mediators and neurotransmitters were compared between the two groups before treatment and after 1 week of treatment. Results: Before treatment, there was no statistically significant difference in serum levels of nerve injury indexes, inflammatory mediators and neurotransmitters between the two groups. After 1 week of treatment, serum nerve injury indexes H-FABP, NT-proBNP, NSE and S100B levels of mild hypothermia group were lower than those of routine group; inflammatory mediators sICAM-1, IL-8, IL-13 and IL-18 levels were lower than those of routine group; neurotransmitter GABA level was lower than that of routine group whereas GABA level was higher than that of routine group. Conclusion: Mild hypothermia + intravenous thrombolysis therapy can effectively reduce the nerve injury and systemic inflammatory response, and optimize the neurotransmitter distribution in patients with acute cerebral infarction.

1. Introduction

Acute cerebral infarction is the most common clinical cerebrovascular disease, the complete or incomplete occlusion of the target vessels leads to cerebral ischemic hypoxic injury, and the secondary edema in local lesion can lead to intracranial pressure and increased nerve injury[1,2]. Reducing target vessel stenosis area and increasing infarct area blood supply by early intravenous thrombolysis is the main method for current treatment of acute cerebral infarction, but there is still significant nerve dysfunction in some patients, which is speculated to be directly related to the prolonged treatment time, a long time of cerebral hypoxia, etc. Decreased oxygen supply and increased oxygen consumption in brain tissue is a pair of contradiction and also the main cause of cerebral hypoxic injury, and it is expected to become the reliable way to improve the brain function by furthest reducing cerebral oxygen consumption at the same time of positive vascular recanalization of infarcted vessels[3,4]. Mild hypothermia is a way to reduce the patient's body temperature by physical methods[5], it has been successfully applied in cardiac surgery, and the therapy was added to the treatment of patients with acute cerebral infarction in the study, and the effect of mild hypothermia combined with intravenous thrombolysis on neural function was explored.

2. Information and methods

2.1 Case information

A total of 176 patients with acute cerebral infarction who were treated in our hospital between September 2015 and February 2017 were selected as the research subjects and divided into the routine group (n=100 cases, receiving routine intravenous thrombolysis therapy) and the mild hypothermia group (n=76, receiving mild...
hypothermia + intravenous thrombolysis therapy) after their therapies were reviewed. There were 58 males and 42 females in the routine group, and they were 59-76 years old; there were 41 males and 35 females in mild hypothermia group, and they were 56-77 years old. The gender and age distribution were not significantly different between the two groups, and the ethics committee of the hospital approved the study plan.

Inclusion criteria: (1) diagnosed with acute cerebral infarction by head CT; (2) with emergency admission within 6 h after cerebral infarction attack; (3) without history of cerebral infarction, cerebral hemorrhage or traumatic brain injury; (4) whose family members signed the informed consent. Exclusion criteria: (1) combined with pneumonia and other systemic infectious diseases; (2) combined with basic severe coagulation dysfunction; (3) combined with neurological disorders such as Alzheimer's disease and Parkinson's disease.

2.2 Therapy

The two groups were routinely monitored for vital signs, mannitol was used to reduce intracranial pressure, and edaravone was used to scavenge oxygen free radicals. Control group also received conventional intravenous thrombolysis, received intravenous drip of urokinase 500 KU and intravenous drip of the solution of 500 KU and 100 mL saline (drip duration < 30 min), and could receive intravenous drip of another 250-500 KU if there was no obvious improvement in clinical symptoms. At the same time of thrombolysis of control group, mild hypothermia group received mild hypothermia treatment, and the specific steps were as follows: cooling cap was used to wrap the patient’s head, the cooling device was started, the water temperature was controlled at 6-12 °C, patient’s tympanic membrane temperature was controlled at 33-35 °C, and the patient’s vital signs and electrolyte levels should be paid close attention to during the period. Rewarming was done in time after mild hypothermia treatment, and 1 °C was elevated every 4-6 h to make the temperature return to 36.5-37.5 °C within 12-20 h.

2.3 Observation indexes

Before treatment and after 1 week of treatment, fasting cubital venous blood serum was obtained from the two groups of patients and stored in a cryogenic environment. ELISA kit was used to detect serum levels of nerve injury indexes heart-type fatty acid-binding protein (H-FABP), N-terminal pro-brain natriuretic peptide (NT-proBNP), neuron-specific enolase (NSE), S100B protein (S100B), inflammatory mediators soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-8 (IL-8), interleukin-13 (IL-13) and interleukin-18 (IL-18) as well as neurotransmitters glutamate (Glu) and γ-aminobutyric acid (GABA).

2.4 Statistical methods

The specific numerical values of nerve injury indexes, inflammatory mediators and neurotransmitters were input in software SPSS 25.0, the statistic P was calculated and P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Nerve injury indexes

Comparison of serum nerve injury indexes H-FABP (pg/mL), NT-proBNP (pg/mL), NSE (ng/mL) and S100B (ng/mL) levels between two groups of patients was as follows: before treatment, serum H-FABP, NT-proBNP, NSE and S100B levels were not significantly different between the two groups of patients (P>0.05). After 1 week

<table>
<thead>
<tr>
<th>Groups</th>
<th>α</th>
<th>Before treatment</th>
<th>After 1 week of treatment</th>
<th>Before treatment</th>
<th>After 1 week of treatment</th>
<th>Before treatment</th>
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<th>Before treatment</th>
<th>After 1 week of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine group</td>
<td>100</td>
<td>27.49±3.51</td>
<td>18.33±2.07</td>
<td>15.28±2.12</td>
<td>9.63±1.04</td>
<td>9.34±0.98</td>
<td>6.18±0.65</td>
<td>10.27±1.63</td>
<td>7.42±0.81</td>
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<td></td>
</tr>
<tr>
<td>Mild hypothermia group</td>
<td>76</td>
<td>27.63±3.48</td>
<td>11.92±1.64</td>
<td>15.31±1.89</td>
<td>5.89±0.61</td>
<td>9.27±0.32</td>
<td>4.07±0.45</td>
<td>10.29±1.58</td>
<td>4.18±0.52</td>
<td></td>
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</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&gt;0.05</td>
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<td>&lt;0.05</td>
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</tbody>
</table>

Note: compared with same group before treatment, *P<0.05.*

Table 2.

Comparison of serum inflammatory mediator levels (pg/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>α</th>
<th>Before treatment</th>
<th>After 1 week of treatment</th>
<th>Before treatment</th>
<th>After 1 week of treatment</th>
<th>Before treatment</th>
<th>After 1 week of treatment</th>
<th>Before treatment</th>
<th>After 1 week of treatment</th>
<th>Before treatment</th>
<th>After 1 week of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine group</td>
<td>100</td>
<td>5.39±0.57</td>
<td>4.12±0.43</td>
<td>7.11±0.76</td>
<td>5.09±0.57</td>
<td>6.23±0.68</td>
<td>4.57±0.53</td>
<td>14.52±1.69</td>
<td>8.42±0.91</td>
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<td></td>
</tr>
<tr>
<td>Mild hypothermia group</td>
<td>76</td>
<td>3.42±0.58</td>
<td>2.76±0.32</td>
<td>7.06±0.75</td>
<td>3.11±0.34</td>
<td>6.19±0.67</td>
<td>2.89±0.37</td>
<td>14.57±1.63</td>
<td>5.27±0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
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</tbody>
</table>

Note: compared with same group before treatment, *P<0.05.*
of treatment, serum H-FABP, NT-proBNP, NSE and S100B levels of both groups were lower than those before treatment; serum H-FABP, NT-proBNP, NSE and S100B levels of mild hypothermia group were lower than those of routine group ($P<0.05$), shown in Table 1.

### 3.2 Inflammatory mediators

Comparison of serum inflammatory mediators sICAM-1, IL-8, IL-13 and IL-18 levels between two groups of patients was as follows: before treatment, serum sICAM-1, IL-8, IL-13 and IL-18 levels were not significantly different between the two groups of patients ($P>0.05$). After 1 week of treatment, serum sICAM-1, IL-8, IL-13 and IL-18 levels of both groups were lower than those before treatment; serum sICAM-1, IL-8, IL-13 and IL-18 levels of mild hypothermia group were lower than those of routine group ($P<0.05$), shown in Table 2.

### 3.3 Neurotransmitters

Comparison of serum neurotransmitters Glu and GABA levels between two groups of patients was as follows: before treatment, serum Glu and GABA levels were not significantly different between the two groups of patients ($P>0.05$). After 1 week of treatment, serum Glu levels of both groups were lower than those before treatment whereas GABA levels were higher than those before treatment; serum Glu level of mild hypothermia group was lower than that of routine group whereas GABA level was higher than that of routine group ($P<0.05$), shown in Table 3.

### 4. Discussion

The root reason for severe neurological impairment caused by acute cerebral infarction is the interruption of oxygen supply in the lesion tissue and the resulting oxidative stress of neurons. Thrombolysis is the basic method to treat acute cerebral infarction, it restores the normal blood supply by infracted vascular recanalization, but a number of studies have shown that ischemia-reperfusion injury after thrombolysis may aggravate the brain edema and brain cell dysfunction. The mild hypothermia is a reliable way to reduce cerebral oxygen consumption, reducing brain edema and avoid ischemia-reperfusion injury after thrombolysis(6), it was used together with the thrombolysis for clinical treatment of patients with acute cerebral infarction in this study, and the influence of the combination therapy on patients' neural function injury was explored in order to provide reference for subsequent treatment selection for such patients.

The vascular occlusion leads to cerebral ischemic hypoxic injury in local lesion of patients with acute cerebral infarction, and the ischemia-reperfusion injury from vascular recanalization after thrombolysis further worsens the neuron damage and nerve dysfunction, which are the primary causes of intelligence and limb dysfunction. The pathological changes of brain tissue can induce the expression of a series of nerve-specific molecules to change, and the specific expression is a reliable means to measure the severity of nerve injury. H-FABP is the main molecule to adjust intracellular fatty acid concentration, it is highly expressed in the brain, skeletal muscle and cardiac muscle, and it may be released from the inside to the outside of the cells after cell damage or apoptosis, which leads to the increased content in local tissue or blood circulation(7,8). NT-proBNP is a sensitive marker for the diagnosis of early cerebral infarction, and the content of NT-proBNP in the circulating blood has rapidly increased after cerebral infarction, which may be because that the water-electrolyte imbalance increases the cerebral edema(9,10). Both NSE and S100B are the most commonly studied neural tissue-specific indexes, they are highly expressed in the nerve cells, but seldom expressed in other tissue viscera, but after nerve injury, the NSE and S100B in the neuron are released into the cerebrospinal fluid, and then enter into the blood through the blood brain barrier whose permeability changes(11,12). The study results showed that compared with those of routine group, serum H-FABP, NT-proBNP, NSE and S100B levels of mild hypothermia group were lower after 1 week of treatment, it indicates that intravenous thrombolysis combined with mild hypothermia can further reduce the nerve injury in patients with acute cerebral infarction, and this is closely related to the cerebral protective mechanisms of mild hypothermia such as lowering cerebral oxygen consumption and inhibiting of oxidative stress reaction.

The injury of any organ is accompanied by inflammation, and the secondary cerebral inflammation after cerebral infarction is one of the main causes of cerebral ischemia-reperfusion injury(13,14). When the blood flow runs through the ischemic area again, a large number of inflammatory mediators will be released, sICAM-1 can prompt the mononuclear macrophage to accumulate in local area and synthesize a large number of inflammatory mediators, and after IL-8, IL-13, IL-18 and other inflammatory factors are synthesized, the local inflammatory reaction is rapidly expanded, the oxidative stress response is triggered, and a large number of oxygen free...
radicals are generated, which further damage the brain [15-17]. The study results showed that compared with those of routine group, serum inflammatory mediators sICAM-1, IL-8, IL-13 and IL-18 levels of mild hypothermia group were lower after 1 week of treatment, it indicates that intravenous thrombolysis combined with mild hypothermia can effectively reduce the cerebral inflammation, and this is also one of the important mechanisms of it to protect the brain tissue.

Under physiological state, the synthesis, release, degradation, reuptake and other processes of the neurotransmitters in brain are strictly regulated by the centre, but when the acute cerebral infarction and nerve dysfunction occur, the synthesis of excitatory neurotransmitters such as Glu increases whereas and the synthesis of inhibitory neurotransmitter GABA relatively decreases, which breaks the neurotransmitter balance and influences the formation of normal nerve impulse and the realization of neural function [18-20].

In the study, the neurotransmitter synthesis was compared between the two groups of patients, and the results showed that compared with those of routine group, serum Glu level of mild hypothermia group was lower whereas GABA level was higher after 1 week of treatment, explaining that thrombolysis combined with mild hypothermia treatment can effectively adjust the neurotransmitter synthesis and release in patients with acute cerebral infarction and help the recovery of patients' neurological function.

Therefore, it is concluded that thrombolysis combined with mild hypothermia can effectively reduce the nerve injury in patients with acute cerebral infarction, the specific mechanisms are associated with its effects on inhibiting inflammation and regulating neurotransmitter synthesis and it is worth popularization and application in clinical practice in the future.

References


[6] Cechmanek BK, Tuor UI, Rushforth D, Barber PA. Very mild hypothermia (35 C) postischemia reduces infarct volume and blood/brain barrier breakdown following TPA treatment in the mouse. Ther


