Effect of low-rTMS in combined with edaravone on the inflammatory cytokines and cerebral metabolites in patients with cerebral infarction and aphasia

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ABSTRACT
Objective: To explore the effect of low-repetitive transcranial magnetic stimulation (low-rTMS) in combined with edaravone on the inflammatory cytokines and cerebral metabolites in patients with cerebral infarction and aphasia. Methods: A total of 70 patients with acute cerebral infarction (ACI) and motor aphasia who were admitted in our hospital from March, 2015 to March, 2016 were included in the study and randomized into the observation group and the control group, 35 in each group. The patients in the control group were given blood pressure reduction, intracranial pressure reduction, blood lipid regulation, anti-platelet aggregation, symptomatic and supportive treatments, edaravone (30 mg) + normal saline (100 mL), ivdrip, 2 times/d, continuously for 2 weeks. On this basis, the patients in the observation group were given additional rTMS, continuously for 10 d. Hs-CRP, IL-6, IL-8, and TNF-α levels before treatment, 1 week and 2 weeks after treatment in the two groups were detected. MRS was used to detect NAA and Cho in Broca district before treatment, 1 week and 2 weeks after treatment in the two groups. ABC was used to evaluate the linguistic function before treatment, 2 weeks, 3 months, and 6 months in the two groups. Results: Hs-CRP, IL-6, IL-8, and TNF-α levels 1 week and 2 weeks after treatment in the observation group were significantly lower than those in the control group (P<0.05). NAA value on the left side 1 week and 2 weeks after treatment in the observation group was significantly higher than that in the control group (P<0.05), while Cho value was significantly lower than that in the control group (P<0.05). ABC score 2 weeks, 3 months, and 6 months after treatment in the observation group was significantly higher than that in the control group (P<0.05). Conclusions: Edaravone in combined with low-rTMS in the treatment of ACI can effectively inhibit the inflammatory reaction, improve the neurological deficit degree, and promote the recovery of cortex language neural network.

1. Introduction

The cerebral infarction is one of the common cerebrovascular diseases in the middle-aged and elderly population. Due to the cerebrovascular occlusion, the cerebral circulation blood supply is blocked, and the brain nerve cells are necrotized due to ischemia and hypoxia, finally leading to neurological deficits in different degrees[1]. Some researches demonstrate that the inflammatory reaction is a main pathological mechanism for delayed neuronal death in patients with acute cerebral infarction (ACI)[2], and is also a main reason for secondary cerebral injury. According to the statistics, the morbidity of aphasia after ACI can reach 21%–38%[3]. Repetitive transcranial magnetic stimulation (rTMS) is a neurotic electrophysiological technology with no pain and non-invasiveness developed on the basis of magnetic stimulation, and has a great potential in the aphasia rehabilitation[4]. The study was aimed to explore the effect of low-rTMS in combined with edaravone on the inflammatory cytokines and cerebral metabolites in patients with cerebral infarction and aphasia.
2. Materials and methods

2.1. Clinical materials

A total of 70 patients with ACI and motor aphasia who were admitted in our hospital from January, 2015 to January, 2016 were included in the study and randomized into the observation group and the control group with 35 cases in each group. In the observation group, 21 were male, and 14 were female; aged from 46 to 70 years old; 17 were merged with hypertension, 6 with diabetes, and 10 with hyperlipidemia. In the control group, 22 were male, and 13 were female; aged from 47 to 71 years old; 15 were merged with hypertension, 7 with diabetes, and 8 with hyperlipidemia. The comparison of gender, age, and complications between the two groups was not statistically significant (\(P>0.05\)).

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) those who were in accordance with the related diagnostic criteria of ACI\(^5\); (2) those who had motor aphasia; (3) those who those who were confirmed by cranial CT or MRI; (4) those who had first onset; (5) those who had normal linguistic function before onset; (6) those who had clear sanity, complete orientation, and normal memory; (7) those who had signed the informed consents. Exclusion criteria: (1) those who had TIA and cerebral hemorrhage; (2) those who had severe heart, liver, and renal dysfunction, and were merged with epilepsy and mental disorders; (3) those who were allergic to related drugs and had detachment.

2.3. Methods

The patients in the control group were given blood pressure reduction, intracranial pressure reduction, blood lipid regulation, anti-platelet aggregation, symptomatic and supportive treatments, edaravone (30 mg) + normal saline (100 mL), ivdrip, 2 times/d, continuously for 2 weeks. On this basis, the patients in the observation group were given additional rTMS. The right hemisphere Broca district was stimulated, with stimulus intensity of 80% of unaffected limb movement threshold value, stimulus frequency of 1 Hz, 10 sequences every day, 50 pulses every sequence, and sequence interval of 120 s. The coil was tangent to the skull surface, and the coil center was placed in the markers, continuously for 10 d.

2.4. Observation indicators

The morning fasting venous blood before treatment, 1 week and 2 weeks after treatment in the two groups was collected. ITA was used to detect hs-CRP; ELISA was used to detect IL-6, IL-8, and TNF-\(\alpha\). MRS was used to detect NAA and Cho in Broca district before treatment, 1 week and 2 weeks after treatment in the two groups. ABC was used to evaluate the linguistic function before treatment, 2 weeks, 3 months, and 6 months in the two groups.

2.5. Statistical analysis

SPSS 19.0 software was used for the statistical analysis. The measurement data are expressed as mean\(\pm SD\), and \(t\) test was used. Chi-square test was used for the enumeration data. \(P<0.05\) was regarded as statistically significant.

3. Results

3.1. Comparison of the serum inflammatory cytokines before and after treatment between the two groups

Hs-CRP, IL-6, IL-8, and TNF-\(\alpha\) levels 1 week and 2 weeks after treatment in the two groups were significantly reduced when compared with before treatment (\(P<0.05\)). Hs-CRP, IL-6, IL-8, and TNF-\(\alpha\) levels 1 week and 2 weeks after treatment in the observation group were significantly lower than those in the control group (\(P<0.05\)) (Table 1).

3.2. Comparison of MRS metabolites before and after treatment between the two groups

NAA value on the left side before treatment in the two groups was significantly lower than that on the right side (\(P<0.05\)), while Cho value was significantly higher than that on the right side (\(P<0.05\)). NAA value on the left side 1 and 2 weeks after treatment in the two groups was significantly elevated, while Cho value was significantly

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>hs-CRP</th>
<th>IL-6</th>
<th>IL-8</th>
<th>TNF-(\alpha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>16.84±3.57</td>
<td>26.37±5.13</td>
<td>50.79±7.36</td>
<td>22.61±5.37</td>
</tr>
<tr>
<td></td>
<td>1 week after treatment</td>
<td>10.24±3.71*</td>
<td>17.58±4.19*</td>
<td>37.75±6.54*</td>
<td>15.35±3.81*</td>
</tr>
<tr>
<td></td>
<td>2 weeks after treatment</td>
<td>6.58±2.34*</td>
<td>10.54±3.43*</td>
<td>19.74±6.38*</td>
<td>9.29±3.48*</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>16.76±3.84</td>
<td>26.52±4.78</td>
<td>51.15±7.25</td>
<td>22.57±5.29</td>
</tr>
<tr>
<td></td>
<td>1 week after treatment</td>
<td>14.42±3.37</td>
<td>21.36±4.51*</td>
<td>42.53±5.31*</td>
<td>18.14±4.22*</td>
</tr>
<tr>
<td></td>
<td>2 weeks after treatment</td>
<td>10.41±2.41*</td>
<td>15.38±3.34*</td>
<td>35.28±7.25*</td>
<td>13.16±3.18*</td>
</tr>
</tbody>
</table>

*\(P<0.05\), when compared with before treatment; \(*\)\(P<0.05\), when compared with the control group.

Table 1
Comparison of the serum inflammatory cytokines before and after treatment between the two groups (\(n=35\), \(\bar{x}\pm s\)).
3.3. Comparison of ABC score before and after treatment between the two groups

ABC score 2 weeks, 3 and 6 months after treatment in the observation group was significantly elevated when compared with before treatment ($P<0.05$). ABC score 3 and 6 months after treatment in the control group was significantly elevated when compared with before treatment ($P<0.05$). ABC score 2 weeks, 3 months, and 6 months after treatment in the observation group was significantly higher than that in the control group ($P<0.05$) (Table 2).

4. Discussion

The brain tissue damage after ACI is mainly associated with the inflammatory reaction caused by ischemia reperfusion injury, while the superoxide free radicals are the factors to initiate the inflammatory reaction, can up regulate the inflammatory cytokine activity, and aggravate the inflammatory reaction[6]. Edaravone, a new type potent oxygen free radical scavenger, can effectively inhibit the lipid peroxidation, enhance the brain tissue perfusion pressure, inhibit the oxidative damage of cerebrovascular endothelial cells, restrain the brain cell apoptosis and neurological function damage, and suppress the production of inflammatory cytokines in order to protect the brain cells and improve the neurological function[7].

rTMS can stimulate the local and distant regions related with functions to realize the regional remodeling of cortex function, affect the central nervous system excitability through frequency regulation, duration, and stimulation interval and intensity, and play a potential therapeutic effect on the nervous system damage[8]. Some researches demonstrate that low-rTMS can inhibit the cerebral cortex, regulate the cortex excitability, promote the synapse adjustment and sprouting to affect the gene expression and the transferring of neurotransmitters, and intervene the network remodeling of cortex function[9].

Some researches demonstrate that the acute inflammatory reaction and ischemia reperfusion injury play an important role in the condition change of ACI, among which hs-CRP, IL-1, IL-6, IL-8, and TNF-α are involved in the inflammatory reaction, and are positively correlated with the severity degree of neurological deficit[10]. Hs-CRP is an acute phase inflammatory reaction protein, can activate the complement system and monocytes, damage the vascular endothelial function, activate the platelet activity, increase the platelet aggregation, increase the risk of thrombogenesis, induce the monocytes to secrete inflammatory mediators, strengthen the pro-inflammatory reaction, promote cerebral ischemia and brain tissue edema in patients with ACI, and aggravate the ischemia and hypoxia degree[11]. IL-6 can activate the neutrophils, strengthen the expression of adhesion molecules in the vascular endothelial cells, aggravate the inflammatory reaction, activate the complement system, promote the release of oxygen free radicals, and cause the apoptosis of cerebral neurons[12]. IL-8 can regulate the inflammatory reaction through the chemotactic effect on neutrophils, release the intracellular enzyme, promote the inflammatory reaction of brain tissues, and is involved in the pathological process of ACI[13]. TNF-α can increase the release of NO and amino acid, produce the free radicals, cause the neurotoxicity, aggravate the oxidative damage, cause the vasoconstriction, aggravate the coagulation state.

Table 2
Comparison of MRS metabolites before and after treatment between the two groups ($n=35$, $\bar{x} \pm s$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>NAA</th>
<th></th>
<th>Cho</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>5.78±2.31$^*$</td>
<td>11.07±0.28</td>
<td>9.52±1.81$^*$</td>
<td>7.56±1.62</td>
</tr>
<tr>
<td></td>
<td>1 week after treatment</td>
<td>7.11±1.52$^*$</td>
<td>11.14±0.32</td>
<td>9.35±1.54</td>
<td>7.48±1.57</td>
</tr>
<tr>
<td></td>
<td>2 weeks after treatment</td>
<td>8.73±2.48$^*$</td>
<td>11.25±0.20</td>
<td>9.27±1.48$^*$</td>
<td>7.41±0.57</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>5.76±2.28$^*$</td>
<td>11.08±0.26</td>
<td>9.53±1.87</td>
<td>7.55±1.63</td>
</tr>
<tr>
<td></td>
<td>1 week after treatment</td>
<td>6.11±1.34$^*$</td>
<td>11.13±0.30</td>
<td>9.43±1.57$^*$</td>
<td>7.46±1.54</td>
</tr>
<tr>
<td></td>
<td>2 weeks after treatment</td>
<td>6.46±2.28$^*$</td>
<td>11.21±0.25</td>
<td>9.34±0.42$^*$</td>
<td>7.44±0.59</td>
</tr>
</tbody>
</table>

$^*P<0.05$, when compared with before treatment; $^\#P<0.05$, when compared with the right side; $^\triangle P<0.05$, when compared with the control group.

Table 3
Comparison of ABC score before and after treatment between the two groups ($n=35$, $\bar{x} \pm s$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before treatment</th>
<th>2 weeks</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>36.79±11.23</td>
<td>46.82±14.21$^*$</td>
<td>67.75±12.69$^*$</td>
<td>78.64±9.37$^*$</td>
</tr>
<tr>
<td>Control group</td>
<td>36.64±12.15</td>
<td>37.39±13.27</td>
<td>46.82±14.27$^*$</td>
<td>56.47±11.26$^*$</td>
</tr>
</tbody>
</table>

$^*P<0.05$, when compared with before treatment; $^\#P<0.05$, when compared with the control group.
increase the risk of cerebral infarction, and aggravate the ischemic brain injury degree[14]. The results in the study showed that hs-CRP, IL-6, IL-8, and TNF-α levels 1 week and 2 weeks after treatment in the observation group were significantly lower than those in the control group (\(P<0.05\)), indicating that edaravone in combined with low-rTMS in the treatment of ACI can effectively inhibit the inflammatory reaction, and improve the neurological deficit degree.

Some researches demonstrate that[15] aphasia after ACI is associated with the direction destruction on linguistic function district or distant effect which refers to that due to the block of connections between the subcortical structure and cortical linguistic function district fibers, the neuronal excitability is reduced, and the afferent fibers access is damaged, with manifestations of reduced local blood flow volume and low metabolism[16]. The left hemisphere damage in patients with aphasia after ACI destroys the inhibition balance of corpus callosum, resulting in the inhibition effect on the unaffected hemisphere weakened or disappeared, and the increased excitability of right hemisphere linguistic district, which is not beneficial for the recovery of linguistic function[17]. Some researches demonstrate that rTMS can improve the imbalance state between the cerebral hemisphere, while low-rTMS acts on the unaffected brain, and has a positive role in promoting the recovery of motor function after cerebral infarction[18]. The results in the study showed that NAA value on the left side 1 week and 2 weeks after treatment in the observation group was significantly higher than that in the control group (\(P<0.05\)), while Cho value was significantly lower than that in the control group (\(P<0.05\); ABC score 2 weeks, 3 months, and 6 months after treatment in the observation group was significantly higher than that in the control group (\(P<0.05\)), indicating that edaravone in combined with low-rTMS in stimulating the linguistic district of unaffected hemisphere can reduce the metabolism level, while the distant effect can increase the metabolism level of linguistic district on the affected side, which can promote the linguistic district of bilateral hemisphere reach in a balance state.

In conclusion, edaravone in combined with low-rTMS in the treatment of ACI can effectively inhibit the inflammatory reaction, improve the neurological deficit degree, and promote the recovery of cortex language neural network.

References