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# Effect of edaravone in combined with rTMS on the free radicals and neurological function in patients with cerebral infarction

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ABSTRACT

**Objective:** To explore the effect of edaravone in combined with repetitive transcranial magnetic stimulation (rTMS) on the free radicals and neurological function in patients with cerebral infarction. **Methods:** A total of 90 patients with acute cerebral infarction (ACI) who were admitted in our hospital from September, 2015 to March, 2016 were included in the study and randomized into the observation group and the control 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 14 d. On this basis, the patients in the observation group were given additional rTMS. 7 d-treatment was regarded as one course, and the patients were treated for 4 courses. The morning fasting venous blood before treatment, 7 d and 14 d after treatment in the two groups was collected to detect NO, NOS, SOD, MDA, S-100 β , and NSE. NIHSS before treatment, 7 d, 14 d, and 28 d after treatment was evaluated. **Results:** NO, NOS, and MDA levels after treatment in the observation group were significantly lower than those in the control group, while SOD level was significantly higher than that in the control group. S-100 β and NSE levels after treatment in the observation group were significantly lower than those in the control group. NIHSS score after treatment in the observation group was significantly lower than that in the control group. **Conclusions:** Edaravone in combined with rTMS in the treatment of ACI can significantly eliminate the free radicals, effectively improve the neurological function, and enhance the long-term efficacy.

## 1. Introduction

With the study on the pathogenesis of acute cerebral infarction (ACI), it is found that the lipid peroxidation damage is closely associated with the white matter lesions of ischemic cerebral vascular disease (ICVD), while the abnormally increased free radicals are the key factors for aggravating the brain tissue damage[1]. Edaravone can effectively eliminate the free radicals in patients with ACI, alleviate the cerebral ischemia-reperfusion damage, protect the brain cells, and improve the neurologic defect function[2]. Repetitive transcranial magnetic stimulation (rTMS) can induce the plastic change of central nervous system, and regulate the local or distant neurological function[3]. The study is aimed to explore the effect of edaravone in combined with rTMS on the free radicals and neurological function in patients with cerebral infarction.

## 2. Materials and methods

### *2.1. Clinical materials*

A total of 90 patients with acute cerebral infarction (ACI) who

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were admitted in our hospital from September, 2015 to March, 2016 were included in the study and randomized into the observation group and the control group with 45 cases in each group. In the observation group, 27 were male, and 18 were female; aged from 45 to 72 years old, with an average age of 60 years old; 19 were merged with hypertension, 7 with diabetes, and 21 with hyperlipidemia. In the control group, 26 were male, and 19 were female; aged from 46 to 72 years old, with an average age of 61 years old; 20 were merged with hypertension, 8 with diabetes, and 19 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[4]; (2) those who those who were confirmed by cranial CT or MRI; (3) those who had signed the informed consents. Exclusion criteria: (1) those who had heart, liver, and renal dysfunction; (2) those who had malignant tumor, immunological disease, severe infection, and bleeding tendency; (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 14 d. On this basis, the patients in the observation group were given additional rTMS. The transcranial magnetic stimulator was used to stimulate DLPFC, with magnetic field intensity of 80%, frequency of 5 Hz, stimulus intensity of 110%, continuously for 20 min, stimulus quantity of 600 pulses, stimulation time of 2 s, interval time of 25 s, 30 sequential rTMS every day, 7 d-treatment as one course, and for 4 courses.

### 2.4. Observation indicators

The morning fasting venous blood before treatment, 7 d and 14 d after treatment in the two groups was collected. The nitric acid reductase method was used to detect NO. The colorimetric method was used to detect NOS. The xanthinoxidase method was used to detect SOD. TBA was used to detect MDA. ELISA was used to detect S-100 β and NSE. NIHSS was used to evaluate the neurological deficit degree before treatment, 7 d, 14 d, and 28 d after treatment, including consciousness, visual field, eye movement, language, cognition, attention, limb movement, sensation, and limb ataxia, with score range of 0-42. The higher the score was, the more serious the neurological deficit degree was.

### 2.5. Statistical analysis

SPSS 19.0 software was used for the statistical analysis. The measurement data were expressed as mean ± 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 free radicals before and after treatment between the two groups

NO, NOS, and MDA levels 7 d and 14 d after treatment in the two groups were significantly reduced ($P$<0.05), while SOD level was significantly elevated when compared with before treatment ($P$<0.05). NO, NOS, and MDA levels after treatment in the observation group were significantly lower than those in the control group ($P$<0.05), while SOD level was significantly higher than that in the control group ($P$<0.05) (Table 1).

### 3.2. Comparison of S-100 β and NSE levels before and after treatment between the two groups

S-100 β and NSE levels 7 d and 14 d after treatment in the two groups were significantly reduced when compared with before treatment ($P$<0.05). S-100 β and NSE levels after treatment in the observation group were significantly lower than those in the control

**Table 1.**

Comparison of the free radicals before and after treatment between the two groups.

| Groups | Time | NO | NOS | SOD | MDA |
|---|---|---|---|---|---|
| Observation | Before treatment | 21.36±1.33 | 92.58±7.38 | 54.73±6.74 | 9.17±1.21 |
| | 7 d after treatment | 15.47±1.76$^{*\Delta}$ | 71.65±6.34$^{*\Delta}$ | 103.13±5.48$^{*\Delta}$ | 5.24±1.15$^{*\Delta}$ |
| | 14 d after treatment | 10.38±1.57$^{*\#\Delta}$ | 57.35±5.62$^{*\#\Delta}$ | 133.27±5.27$^{*\#\Delta}$ | 3.27±1.11$^{*\#\Delta}$ |
| Control | Before treatment | 21.38±1.64 | 92.48±7.24 | 54.57±6.82 | 9.18±1.20 |
| | 7 d after treatment | 17.24±1.35$^{*}$ | 85.61±6.72$^{*}$ | 83.26±5.43$^{*}$ | 7.36±1.21$^{*}$ |
| | 14 d after treatment | 13.54±1.78$^{*\#}$ | 72.65±6.41$^{*\#}$ | 102.34±6.17$^{*\#}$ | 5.23±1.35$^{*\#}$ |

$^{*}P$<0.05, when compared with before treatment; $^{\#}P$<0.05, when compared with 7 d after treatment; $^{\Delta}P$<0.05, when compared with the control group.

group ($P$<0.05) (Table 2).

**Table 2.**

Comparison of S-100 β and NSE levels before and after treatment between the two groups.

| Groups | Time | S-100 β protein | NSE |
|---|---|---|---|
| Observation | Before treatment | 1.78±0.35 | 25.46±4.16 |
| | 7 d after treatment | 0.68±0.16$^{*\Delta}$ | 11.37±2.62$^{*\Delta}$ |
| | 14 d after treatment | 0.35±0.15$^{*\#\Delta}$ | 4.68±2.34$^{*\#\Delta}$ |
| Control | Before treatment | 1.77±0.36 | 24.88±4.51 |
| | 7 d after treatment | 0.89±0.23$^{*}$ | 15.52±3.48$^{*}$ |
| | 14 d after treatment | 0.65±0.17$^{*\#}$ | 10.54±3.57$^{*\#}$ |

$^{*}P$<0.05, when compared with before treatment; $^{\#}P$<0.05, when compared with 7d after treatment; $^{\Delta}P$<0.05, when compared with the control group.

### *3.3. Comparison of NIHSS score before and after treatment between the two groups*

NIHSS score 7 d, 14 d, and 28 d after treatment in the two groups was significantly reduced when compared with before treatment ($P$<0.05). NIHSS score after treatment in the observation group was significantly lower than that in the control group ($P$<0.05) (Table 3).

**Table 3.**

Comparison of NIHSS score before and after treatment between the two groups.

| Groups | Before treatment | 7 d after treatment | 14 d after treatment | 28 d after treatment |
|---|---|---|---|---|
| Observation | 15.64±5.34 | 11.35±3.17$^{*\blacktriangle}$ | 8.64±3.27$^{*\#\blacktriangle}$ | 5.28±2.51$^{*\#\Delta\blacktriangle}$ |
| Control | 15.81±5.17 | 13.28±3.24$^{*}$ | 10.75±3.22$^{*\#}$ | 7.97±3.16$^{*\#\Delta}$ |

$^{*}P$<0.05, when compared with before treatment; $^{\#}P$<0.05, when compared with 7 d after treatment; $^{\Delta}P$<0.05, when compared with 14 d after treatment; $^{\blacktriangle}P$<0.05, when compared with the control group.

## 4. Discussion

The blood circulation disorder of brain tissues is involved in patients with ACI due to intracranial arterial thrombosis or other reasons, characterized by intraceullar calcium ion overloading and brain cell degenerative necrosis[5]. After cerebral infarction, the brain tissue damage is mainly associated with the inflammatory reaction caused by ischemia reperfusion, among which 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 is a new type oxygen free radical scavenger, can penetrate the blood brain barrier, effectively inhibit the oxidative damage of cerebrovascular endothelial cells, enhance the brain tissue perfusion pressure, inhibit the brain cell apoptosis and neurological function damage, and rapidly protect the brain tissues[7]. Edaravone can inhibit the lipid peroxidation, eliminate the free radicals, restrain the oxidative damage of neurons, brain cells, and vascular endothelial cells, and prevent the progression of hydrocephalus and cerebral infarction in order to improve the neurological function[8].

The normal brain bilateral hemisphere cortex function is in a balance state. The interhemisphere connection and association fibers are mutually synergized and inhibited. When there is a local ischemia, the excitability of affected hemisphere is reduced, while the inhibiting effect of unaffected hemisphere is relatively strengthened, and the inhibition imbalance and excitability asymmetry occur between the bilateral hemispheres, which can affect the motor function recovery of affected hemisphere; therefore, regulating the excitability of cerebral cortex to improve the imbalance state between the bilateral cerebral hemispheres in order to promote the function recovery after cerebral infarction[9]. rTMS is a neurotic and electrophysiological stimulation technology developed on the basis of transcranial magnetic stimulation, can induce the cerebral deep induced current by taking advantage of the time varying magnetic field with a certain intensity, stimulate the excitable tissues, 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[10].

NO is a kind of neurotoxic free radical, can combined with superoxide anions to form ONOO, and is involved in the lipid peroxidation damage[11]. In normal individuals, the serum NO content is less. ACI can activate NOS and catalyze the synthesis of NO, which can cause the neuronal death and brain tissue damage[12]. SOD can reduce the damage of free radicals to the brain tissues, and decrease the production of peroxides when there is a reperfusion. In patients with ACI, the free radicals are greatly enhanced, resulting in the excessive consumption and reduced expression of SOD[13]. MDA can indirectly reflect the free radical level, is the most important product of lipid peroxidation, and is an important indicator to evaluate the lipid peroxidation degree[14]. The results in the study showed that NO, NOS, and MDA levels after treatment in the observation group were significantly lower than those in the control group ($P$<0.05), while SOD level was significantly higher than that in the control group ($P$<0.05), indicating that edaravone in combined with rTMS can effectively eliminate the free radicals, enhance the antioxidant ability, and improve the neurological function.

S-100 β protein is mainly distributed in the neuroglias and Schwann cells of peripheral and central nervous system, and is a landmark protein of neuroglias. In the early stage of ACI, the blood brain barrier is damaged, resulting in the destruction of cell membrane integrity, and a large amount of S-100 β protein releasing into the blood circulation; therefore, it is argued that S-100 β protein can be served as a specific marker of central nervous system damage, whose change can reflect the neurocyte damage degree[15,16]. NSE exists in the cytoplasm of neurons. When ischemia and hypoxia occur in the central nervous system, the cell membrane of neurons is damaged, and NSE is released into the intercellular space, and enters

the cerebrospinal fluid and blood, resulting in the elevation of serum NSE level; therefore, it is argued that NSE can sensitively reflect the neuron damage degree, and is a unique specific marker to reflect the neuron damage[15,17]. The results in the study showed that S-100 β and NSE levels after treatment in the observation group were significantly lower than those in the control group ($P<0.05$); NIHSS score after treatment in the observation group was significantly lower than that in the control group ($P<0.05$, indicating that edaravone in combined with rTMS can significantly improve the neurological function, and enhance the long-term therapeutic effect.

In conclusion, edaravone in combined with rTMS in the treatment of ACI can significantly eliminate the free radicals, effectively improve the neurological function, and enhance the long-term efficacy.

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