

Original Article

Effects of low-frequency repetitive transcranial magnetic stimulation combined with nicergoline in the treatment of post-ischemic stroke depression

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Abstract: Objective: To investigate the effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) combined with nicergoline on serum nerve growth factor (NGF) and serotonin (5-HT) levels and quality of life in patients with post-stroke depression (PSD). Methods: A total of 113 patients with PSD from January 2015 to June 2017 were enrolled and divided into the control group (CG, n = 56) treated with nicergoline and the study group (SG, n = 57) treated with rTMS plus nicergoline. The clinical efficacy, serum NGF, 5-HT levels, adverse reactions, degree of depression (HAMD), neurological function (NIHSS), quality of life (WHOQOL-100) scores, inflammatory cytokine levels and fitness level were compared between the two groups. Results: The total effective rate of the SG was 91.23% (52/57), higher than 76.79% (43/56) of the CG ($P < 0.05$). The levels of serum NGF and 5-HT in the SG were higher than those in the CG after 1 month of treatment ($P < 0.05$). The SG showed lower HAMD and NIHSS scores and higher WHOQOL-100 score than the CG after 1 month of treatment ($P < 0.05$). The SG also exhibited higher Fugl-Meyer Assessment (FMA) scores in upper and lower extremity, BBS scores and lower serum IL-6, TNF- α , hs-CRP levels than the CG ($P < 0.05$). The total incidence of adverse reactions in the SG was 10.53% (6/57), which was not significantly different from 5.36% (3/56) in the CG ($P > 0.05$). Conclusion: rTMS combined nicergoline has antidepressive effect and improves nerve function, fitness level, inflammation level and serum NGF, 5-HT levels as well as quality of life in patients with PSD.

Keywords: Low-frequency repetitive transcranial magnetic stimulation, nicergoline, post-stroke depression, nerve growth factor, serotonin

Introduction

Post-stroke depression (PSD) is one of the common sequelae of ischemic stroke [1]. Statistics showed that 37% of patients with ischemic stroke will develop depression [2, 3]. Depression can prolong the recovery, greatly affecting the prognosis and quality of life [4, 5]. Nicergoline is an ergot derivative used in the treatment of PSD and senile dementia, which can significantly increase the oxygen and energy supply and improve blood circulation in the brain [6]. Low-frequency repetitive transcranial magnetic stimulation (rTMS) can regulate the neurotransmitters and the expression of many genes by converting magnetic signals into electrical signals. It also regulates the function of neurons, improves the function of the cerebral

cortex, and promotes local functional reconstruction, thereby improving the cognitive, motor, language, and emotional functions [7]. Nerve growth factor (NGF) is one of the most important neurotrophic factors, protecting nerve cells. Serotonin (5-HT) is an inhibitory neurotransmitter that has been found to be intimately involved in emotion and mood. It participates in and mediates a variety of neural activities and has the functions of regulating memory, learning, eating and mood [8]. The level of inflammatory response plays an important role in the pathophysiology of ischemic stroke, and it is also related to the occurrence of depression, but the specific mechanism remains unclear [9]. At present, there are many clinical reports on the efficacy of rTMS combined with nicergoline in the treatment of PSD [10], but

few reports on the effects on the levels of serum NGF and 5-HT in patients. Therefore, this study was grouped to investigate the effects of rTMS combined with nicergoline on serum NGF and 5-HT levels and quality of life in patients with PSD, and to explore the mechanism of action, so as to provide a reference for the clinical development of therapeutic regimen for PSD.

Materials and methods

Baseline data 113 cases of patients with PSD in our hospital from January 2015 to June 2017 were divided into the control group (CG, n = 56) and the study group (SG, n = 57) by random number table method. Among them, the CG included 33 males and 23 females, with the average age of (63.28±5.91) years, while the SG included 36 males and 21 females, with the average age of (63.67±6.04) years. This study was approved by the Ethics Committee of Inner Mongolia Baogang Hospital.

Selection criteria

Inclusion criteria: patients (1) who were clinically diagnosed as PSD [11, 12]; (2) whose family signed the written consent form.

Exclusion criteria: patients (1) with severe depression and suicidal tendencies; (2) complicated with severe physical illness; (3) with tumor; (4) with history of brain surgery; (5) prone to cerebral hemorrhage; (6) equipped with pacemaker; (7) with low compliance.

Methods

The CG was orally treated with nicergoline (Hainan Shatingning Pharmaceutical Co., Ltd., approval number: H20055907, 10 mg), t.i.d. The SG was additionally treated with rTMS with YRD CCY-1 transcranial magnetic stimulator (Wuhan Yiruide Medical Co., Ltd.) with a stimulation intensity of 80% MT, a stimulation frequency of 10 Hz, and a magnetic field intensity of 1.2 T. The metal objects were removed from the patient and the coil was placed on the top of head and a magnetic field was applied to the whole brain for 20 min, 5 times/week. Both groups were treated continuously for 1 month.

Detection method: 4 ml of fasting venous blood samples were collected, and centrifuged (2500 r/min, 5 min) to obtain the supernatant. Serum NGF and 5-HT levels were measured by enzyme-

linked immunosorbent assay. The kit was purchased from Shanghai Yifeng Biotechnology Co., Ltd.

Efficacy evaluation: Invalid is defined as HAMD score reduction of < 50%; remission is 50% to 75%; cure is > 75%, and remission and cure were calculated as the total effective rate.

Outcome measurement: (1) Clinical effects. (2) The levels of serum NGF and 5-HT in both groups before treatment and after 1 month of treatment were measured. (3) Before treatment and after 1 month of treatment, the degree of depression was evaluated by the Hamilton Depression Scale (HAMD), the neurological function was evaluated by the Stroke Scale (NIHSS), and the quality of life was assessed by WHO QOL-100 in the two groups. (4) Before and after 1 month of treatment, Fugl-Meyer Assessment (FMA) scale and Berg Balance Scale (BBS) were used to evaluate the fitness level of the two groups. (5) Before treatment and 1 month of treatment, 3 ml of fasting venous blood samples were collected and centrifuged. The serum interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), hypersensitive C-reactive protein (hs-CRP) were measured in the two groups using an automatic biochemical analyzer. (6) The incidence of adverse reactions (including dry mouth, insomnia, and headache) was recorded in two groups.

Statistical analysis

With SPSS 23.0, measurement data (serum NGF, 5-HT level, HAMD, NIHSS, WHOQOL-100 score) were represented by ($\bar{x} \pm s$) and were tested by *t* test. Count data were represented by *n* (%) and were examined by chi-square test. Grade data were compared by rank sum test. *P* < 0.05 was considered statistically significant.

Results

Comparison of baseline data

No statistically significant difference was found in the clinical data of the two groups, including gender, age, HAMD score and NIHSS score (*P* > 0.05) (**Table 1**).

Comparison of clinical effect

The total effective rate of the SG was 91.23%, higher than that of the CG, 76.79%, (*P* < 0.05),

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Table 1. Comparison of baseline data

Grouping	n	Male/Female	Age (year)	HAMD score	NIHSS score
Control group	56	33/23	63.28±5.91	28.06±2.71	32.97±5.03
Study group	57	36/21	63.67±6.04	27.87±2.34	32.51±4.67

Table 2. The clinical effect of two groups [n (%)]

Grouping	Number of cases	Invalid	Reemission	Cure	Total effective rate
Study group	57	5 (8.77)	29 (50.88)	23 (40.35)	52 (91.23)
Control group	56	13 (23.21)	31 (55.36)	12 (21.43)	43 (76.79)
u/χ^2			2.382		4.399
<i>P</i>			0.017		0.035

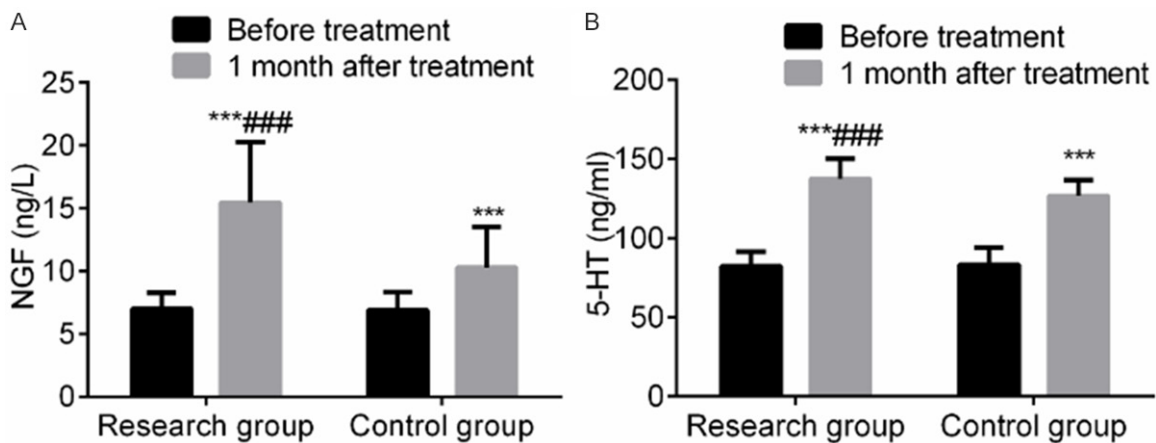


Figure 1. Comparison of serum NGF and 5-HT levels between the two groups. Note: Compared with before treatment, ****P* < 0.001, compared with before treatment, ###*P* < 0.001.

suggesting that rTMS combined with nicergoline can significantly improve the clinical efficacy in patients with PSD (**Table 2**).

Comparison of serum NGF and 5-HT levels

Before treatment, there was no statistically significant difference in serum NGF and 5-HT levels between the two groups (*P* > 0.05). After 1 month of treatment, the levels of serum NGF and 5-HT in the SG were significantly higher than those in the CG (*P* < 0.05). The serum NGF and 5-HT levels in the SG were higher than those in the CG after 1 month of treatment (*P* < 0.05). It is suggested that rTMS combined with nicergoline can significantly improve the levels of NGF and 5-HT in patients with PSD (**Figure 1**).

Comparison of HAMD, NIHSS and WHOQOL-100 scores

No significant difference was found among the HAMD, NIHSS and WHOQOL-100 scores

between the two groups before treatment (*P* > 0.05). The HAMD and NIHSS scores were decreased in both groups after treatment, and the WHOQOL-100 score was higher than that before treatment (*P* < 0.05). Moreover, the scores of HAMD and NIHSS in the SG were lower than those in the CG, and the WHOQOL-100 score in the SG was higher than that in the CG (*P* < 0.05). It is suggested that rTMS combined with nicergoline can significantly improve the HAMD, NIHSS and WHOQOL-100 scores of patients with PSD (**Figure 2**).

Comparison of fitness level between the two groups

Before treatment, there was no significant difference in FMA scores of upper extremities and lower extremities, and BBS scores between the two groups (*P* > 0.05). After 1 month of treatment, FMA scores of upper extremities and lower extremities as well as BBS scores were increased in the two groups than those before

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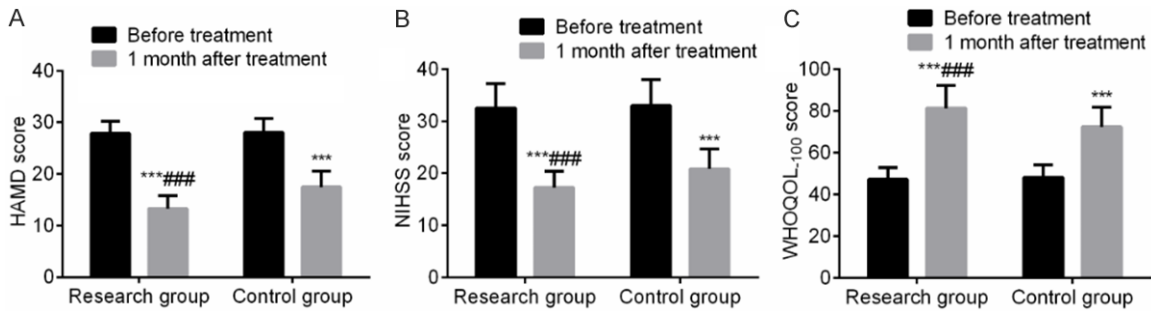


Figure 2. Comparison of HAMD, NIHSS and WHOQOL-100 scores between the two groups. Note: Compared with before treatment, *** $P < 0.001$, compared with before treatment, ### $P < 0.001$.

Table 3. Fitness level of the two groups ($\bar{x} \pm s$, minutes)

Time	Grouping	Number of cases	Upper limb FMA score	Lower limb FMA score	BBS score
Before treatment	Study group	57	23.42±5.31	12.13±3.21	16.62±7.93
	Control group	56	23.05±5.19	11.87±3.08	16.19±8.32
	<i>t</i>		0.375	0.439	0.281
	<i>P</i>		0.708	0.662	0.779
After 1 month of treatment	Study group	57	36.21±6.54	18.27±3.85	31.56±9.53
	Control group	56	32.32±6.02	15.85±3.60	25.46±8.38
	<i>t</i>		3.288	3.450	3.611
	<i>P</i>		0.001	0.001	0.000

treatment ($P < 0.05$). FMA score of the upper and lower extremities, and the BBS score of the SG were higher than those of the CG after 1 month of treatment ($P < 0.05$). It is suggested that rTMS combined with nicergoline can significantly improve the fitness level of patients with PSD (**Table 3**).

Comparison of the levels of inflammatory cytokines

Before treatment, there was no significant difference in serum IL-6, TNF- α , hs-CRP levels between the two groups ($P > 0.05$). The levels of serum IL-6, TNF- α and hs-CRP in the two groups after 1 month of treatment were lower than those before treatment ($P < 0.05$). The levels of serum IL-6, TNF- α , and hs-CRP in the SG were lower than those in the CG after 1 month of treatment ($P < 0.05$). It is suggested that rTMS combined with inflammatory cytokines can significantly improve the level of inflammatory cytokines in patients with PSD (**Table 4**).

Adverse reactions

The total incidence of adverse reactions in the SG and CG were 10.53% and 5.36% ($P >$

0.05), suggesting that rTMS combined with nicergoline did not increase adverse reactions in patients with PSD (**Table 5**).

Discussion

The mechanism of PSD is not yet clear. It may be related to the disorder of metabolic metabolism of biogenic amines in the brain tissue and changes in the prefrontal cortical circuits [13, 14]. Depression hinders the recovery of neurological deficits in patients with ischemic stroke, and timely antidepressant treatment can significantly improve the neurological function and prolong survival [15]. Monoamine oxidase inhibitors were used in the treatment of depression, but the overall effect is poor.

Nicergoline is a potent vasodilator. At the cerebral level, it prompts a lowering of vascular resistance, an increase in arterial flow and stimulates the use of oxygen and glucose. Hua et al. [16] found that when patients with migraine were treated with nicergoline, the reduction rates of anxiety and depression scores were 54.15% and 42.60%, respectively, and the total response rate of treatment was 72.30%. In this study, the application of nicer-

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Table 4. Comparison of inflammatory cytokines in the two groups ($\bar{x} \pm s$)

Time	Grouping	Number of cases	IL-6 (ng/L)	TNF- α (ng/L)	hs-CRP (mg/L)
Before treatment	Study group	57	91.52 \pm 11.24	140.87 \pm 14.95	5.61 \pm 2.33
	Control group	56	92.41 \pm 11.09	141.57 \pm 14.52	5.68 \pm 2.21
	<i>t</i>		0.424	0.252	0.164
	<i>P</i>		0.672	0.802	0.870
After 1 month of treatment	Study group	57	50.73 \pm 8.23	83.86 \pm 9.53	2.95 \pm 1.68
	Control group	56	72.46 \pm 10.42	103.43 \pm 10.77	3.83 \pm 1.94
	<i>t</i>	-	12.314	10.234	2.579
	<i>P</i>	-	< 0.001	< 0.001	0.011

Table 5. Comparison of adverse reactions in the two groups [n (%)]

Grouping	Number of cases	Dry mouth	insomnia	headache	Total incidence
Study group	57	0 (0.00)	3 (5.26)	3 (5.26)	6 (10.53)
Control group	56	2 (3.57)	1 (1.79)	0 (0.00)	3 (5.36)
χ^2					0.445
<i>P</i>					0.504

goline in patients with PSD can effectively activate the 5-HT receptor in the synaptic space, make it secrete related neurotransmitters, transmit nerve signals, and then exert antidepressant effects. Depression is closely related to the change in excitability of the cerebral cortex. Therefore, threshold for nerve cell excitement in the cerebral cortex could be regulated for the treatment of PSD [17]. Chen et al. [18] have proved that high-frequency and low-frequency rTMS therapies in Parkinson's disease patients can significantly improve their depression, fatigue and mental state, improve sleep quality, and effectively shorten the total time taken in 10 Meter Walking Test. rTMS targets forehead and limbic system of the brain, improves the excitability threshold of nerve cells in the cerebral cortex, increases the levels of glutamate, dopamine and other neurotransmitters, thereby improving the excitability of the cerebral cortex. It can also promote cortical reconstruction, brain frontal lobe metabolism and blood circulation, correct brain imbalance, thus effectively promoting the recovery of limb motor function. Ma et al. [19] reported that rTMS can effectively improve tinnitus symptoms and sleep quality in patients with subjective tinnitus, with a total effective rate of 60.00%. Transcranial magnetic stimulation (TMS) is a non-invasive procedure that uses magnetic fields to stimulate nerve cells in the brain to improve symptoms of depression. TMS

is typically used when other depression treatments have failed [20-22]. This study showed that the total effective rate of the SG was higher than that of the CG, and the HAMD and NIHSS scores of the SG were lower than that of the CG after 1 month of treatment ($P < 0.05$), demonstrating that nicergoline combined with rTMS has a significant effect in patients with PSD, which significantly improves their depression and nerve function.

NGF is one neurotrophic factor that has the function of protecting nerve cells. Studies have shown that serum NGF levels in patients with stroke are significantly reduced, which is closely related to the occurrence of DPS [23]. 5-HT is one of the inhibitory neurotransmitters. It involves in and mediates some neural activities. It has the functions of regulating memory, learning, eating and mood. When the body is under stress, the secretion of 5-HT and its receptors is significantly reduced, and the neurogenesis of the dentate gyrus is slowed down, which in turn leads to depression and other mental system diseases [24]. This study showed that levels of serum NGF and 5-HT in the SG was higher than that in the CG after 1 month of treatment ($P < 0.05$), the WHOQOL-100 score in the SG was higher than that in the CG ($P < 0.05$), and the total incidence of adverse reactions was reduced in both groups, demonstrating that nicergoline combined with rTMS

can significantly increase serum NGF and 5-HT levels, improve the quality of life, with higher safety.

Most patients with ischemic stroke are accompanied by a certain degree of dyskinesia, which may lead to depression. The research results of Zhao et al. [25] showed that the Fugl-Meyer score and Berg score of stroke patients with motor dysfunction were significantly improved after rTMS treatment. The effectiveness of rTMS in the treatment of dyskinesia following stroke has been clinically proven, but opinions are divided on the parameters setting of rTMS. Some scholars believe that the effect of high-frequency rTMS is better than that of low-frequency rTMS, and some scholars hold the opposite view, and some scholars believe that the two options are equally effective. The results of this study showed that the FMA scores of the upper extremities, the FMA score of the lower extremities, and the BBS score of the SG were higher than those of the CG after 1 month of treatment, indicating that the low-frequency rTMS has a definite effect on dyskinesia after stroke. The reason may be that low-frequency rTMS can regulate the inhibitory response between the two hemispheres, inhibit the excitability of the healthy hemisphere, and help balance the brain function on both sides.

Some studies have found that IL-6, TNF- α , hs-CRP have relationship with the occurrence of PSD, and the inflammatory response may lead to changes in emotion, physiology, cognition, etc. [26]. Patients with PSD have higher levels of inflammatory cytokines such as IL-6, TNF- α , and hs-CRP, which can inhibit 5-HT levels, cause neuro-endocrine immune system disorders and aggravate negative emotions in patients. The results of this study showed that the levels of serum IL-6, TNF- α and hs-CRP in the SG were lower than those in the CG after 1 month of treatment, suggesting that nicergoline combined with rTMS in patients with PSD can improve inflammation response, but the specific anti-inflammatory mechanism is not yet clear, and further research is needed.

To sum up, the combination of nicergoline and rTMS can significantly improve depression, nerve function and serum NGF and 5-HT levels, fitness level, reduce inflammation and improve quality of life with high safety in patients with PSD. However, the sample size in this study is

small, and long-term follow-up studies of multi-channel and multi-center sample are needed.

Disclosure of conflict of interest

None.

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