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Original Article

The effect of fluoxetine combined with repetitive transcranial magnetic stimulation on the psychological emotions and cognitive and neurological functions of acute post-stroke depression patients

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Abstract: Objective: This research was designed to probe into the effects of fluoxetine combined with repetitive transcranial magnetic stimulation (rTMS) on the psychological emotions and the cognitive and neurological functions of acute post-stroke depression patients. Methods: This experiment recruited 115 acute post-stroke depression patients who were treated in our hospital from February 2018 to April 2020 as the study cohort. 55 of the patients were treated with fluoxetine, and 60 were treated with fluoxetine combined with rTMS. Both groups were treated for 2 months. The self-rating anxiety scale (SAS), the self-rating depression scale (SDS), the National Institutes of Health stroke scale (NIHSS), the mini mental state scale (MMSE), the Barthel index, and the quality of life scale (SF-36) scores were observed. Results: Compared with the control group (CG), the SAS, SDS, and NIHSS scores in the research group (RG) decreased, while the MMSE and Barthel index scores increased ($P < 0.05$). After the treatment, the SF-36 scores in the RG were higher than they were in the CG ($P < 0.05$). Conclusion: Fluoxetine combined with rTMS can effectively improve the psychological emotions and the cognitive and neurological functions of acute post-stroke depression patients, so it is worthy of clinical promotion.

Keywords: Fluoxetine, repetitive transcranial magnetic stimulation, acute stroke, psychological emotion, cognitive function, neural function

Introduction

Stroke, known as apoplexy and cerebrovascular accident, is an acute cerebral vessel disease. It is a set of diseases that brings about brain tissue damage because of a sudden rupture of the blood vessels in the brain or because of blood vessel blockage and includes ischemic and hemorrhagic stroke. The morbidity of ischemic stroke is higher than that of hemorrhagic stroke, making up 60%-70% of the total [1, 2]. Strokes are common among middle-aged and elderly people [3]. Strokes are now occurring more often among younger people, with more and more stroke patients under 40 years old [4, 5]. Stroke is characterized by an acute onset, rapid deterioration, and a poor prognosis. Because it often causes damage to the brain center, it's common for stroke patients to suffer from body dysfunction [6, 7]. With the continuous changes in people's diets and lifestyles, the incidence of the disease is increasing year by year. Post-stroke depression is a familiar complication of this disease, with an incidence of 25%-75%. It leads to changes in patients' mood and also adversely affects their cognitive function [8-10]. Thus, the rehabilitation treatment of stroke patients has always been a hot research project clinically.

Fluoxetine is a widely-used selective 5-HT reuptake inhibitor. But its efficacy is variable and incomplete: 60%-70% of patients have no remission, and 30%-40% have no obvious reaction [11, 12]. Repetitive transcranial magnetic stimulation (rTMS) is a neural stimulation and regulation procedure that uses the principle of electromagnetic induction of the brain's electric

field. The magnetic field is large and dense enough to depolarize neurons [13]. rTMS has been found to be a promising noninvasive treatment for many neuropsychiatric diseases, such as depression, nervous system diseases, aphasia after stroke or the rehabilitation of hand function [14, 15]. At the moment, fluoxetine combined with rTMS has not been studied on post-stroke depression. So, we analyzed the effects of fluoxetine combined with rTMS on post-stroke depression, providing information for clinical practice.

Materials and methods

Basic data

In this experiment, 115 acute post-stroke depression patients who were treated at the People's Hospital of Liaoning Province from February 2018 to April 2020 were recruited as the study cohort. 55 of the patients were treated with fluoxetine, and 60 were treated with fluoxetine combined with rTMS. Both groups were treated for 2 months. The study was approved by the medical ethics committee of our hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows: patients who met the clinical diagnosis and whose related diagnosis was confirmed as stroke, patients 45-65 years old, patients with complete general clinical data, patients who agreed to cooperate with and assist the medical staff in our hospital to complete the investigation, and patients who signed the informed consent forms.

The exclusion criteria were as follows: patients who quit the experiment halfway, patients comorbid with malignancies or severe organ dysfunction, people with infectious diseases, poor treatment compliance, a physical disability, and patients who transferred from one hospital to another.

Treatment plan

After admission, the patients in both groups were administered routine treatment for acute stroke, including anti-platelet aggregation, protection of the brain cells and symptomatic support, and routine functional recovery training.

The patients in the CG were given fluoxetine (specification 20 mg, manufacturer: Patheon France, France; SFDA approval No. J20170022) orally, 20 mg once a day.

The RG was treated with rTMS in addition to the treatment administer to the CG. Rapid2, a transcranial magnetic stimulation system produced by Magstim in Britain, was selected as the instrument. The standard "8"-shaped double coils were put into use, and the magnetic field intensity was set to 2.2T. During the treatment, the patient kept a comfortable position and relaxed the whole body. The lower jaw was placed on the fixed bracket, and the position of the magnetic stimulation coil was adjusted so that its center was on the dorsolateral side of the left prefrontal lobe and tangent to the scalp. The frequency of magnetic stimulation was set to 10 Hz, and the intensity was 90% of the motion threshold. Each stimulation time of a single sequence was 4 s, and 20 sequences were stimulated every day, 3 times per week. Both groups were treated continuously for 8 weeks.

Scoring criteria

The patients' mental health was tested using the self-rating anxiety scale (SAS) and the self-rating depression scale (SDS). The SAS scale is 100 points in total. After the treatment, 50-70 indicates mild anxiety, 71-90 indicates moderate anxiety, and > 90 indicates severe anxiety. The higher the score, the more serious the postpartum anxiety is. The SDS scale is 100 points in total. After the treatment, 50-70 indicates mild depression, 71-90 indicates moderate depression, and > 90 indicates severe depression. The functional status of the activities of daily living (ADL) was tested using the Barthel index, 100 points possible. The higher the score, the stronger the patients' ADL is. It was also evaluated through the National Institutes of Health stroke scale (NIHSS), including consciousness level, gaze, visual field, limb movement, ataxia, feeling, language, etc.. The total score ranges from 0-42 points: scores ≤ 15 denote mild neurological impairment, 16-20 indicates moderate, and > 20 indicates severe. The patients' cognitive function was analyzed using the mini-mental state examination (MMSE). 30 points is the highest: 27-30 is normal, and < 27 indicates cognitive dysfunction. The patients' quality of life was evaluated using the SF-36 scale. It is divided into eight dimensions: physical health (physiological function, physiological role, physical pain, general health) and mental health (vitali-

Table 1. Basic clinical data [n (%)]

	Research group (n=60)	Control group (n=55)	χ^2 or t	P
Age (years)	55.91±8.76	55.75±9.02	0.097	0.923
BMI	21.05±1.24	21.02±1.17	0.133	0.894
History of smoking			0.011	0.915
Yes	42 (70.00)	39 (70.91)		
No	18 (30.00)	16 (29.09)		
History of drinking			0.807	0.369
Yes	31 (51.67)	33 (60.00)		
No	29 (48.33)	22 (40.00)		
Place of residence			0.168	0.682
Cities	35 (58.33)	30 (54.55)		
Countryside	25 (41.67)	25 (45.45)		
Education level			0.515	0.773
Primary school and below	14 (23.33)	16 (29.09)		
Junior high school or high school	36 (60.00)	30 (54.55)		
University and above	10 (16.67)	9 (16.36)		
Disease type			0.046	0.831
Cerebral hemorrhage	25 (41.67)	24 (43.64)		
Cerebral infarction	35 (58.33)	31 (56.36)		
Course of disease (d)	27.58±4.51	27.02±5.20	0.618	0.538

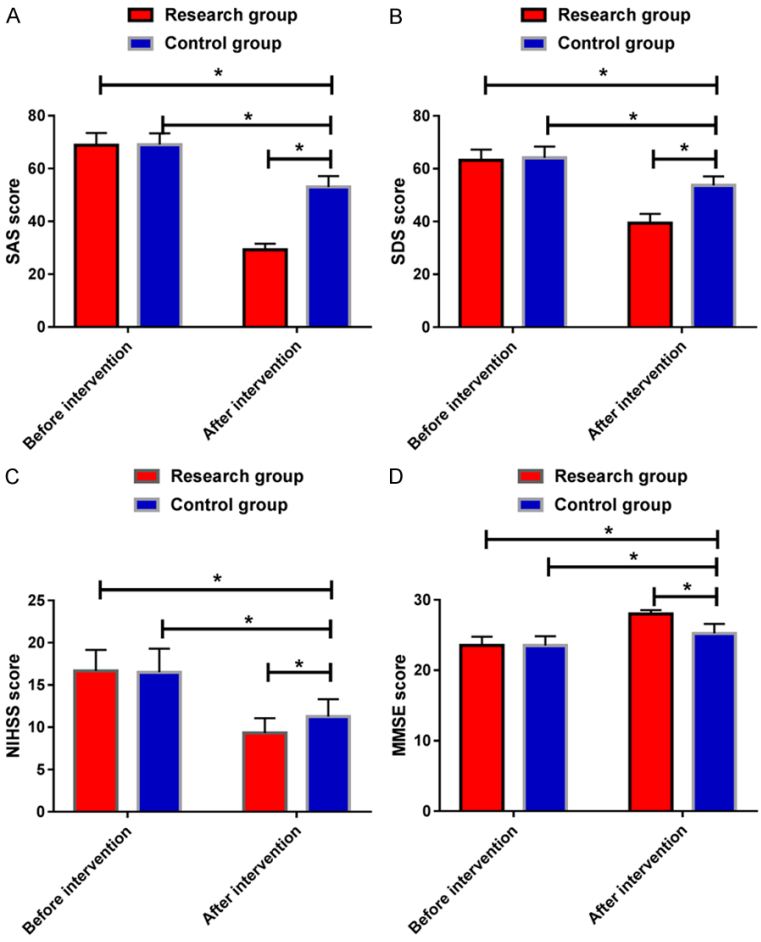

Figure 1. The SAS, SDS, NIHSS, MMSE scores. A. The SAS scores in the RG were decreased after the treatment and were lower than the SAS scores in the CG. B. The SDS scores in the RG were decreased after the treatment and were lower than the scores in the CG. C. The NIHSS scores in the RG decreased after the treatment and were lower than they were in the CG. D. The MMSE scores in the RG increased after the treatment and were higher than they were in the control group. Note: * indicates that there is a significant difference between the two groups ($P < 0.05$).

ty, social function, role emotional), each dimension has a maximum possible score of 100 points, and the higher the score, the better the quality of life.

Outcome measures

The main outcome measures were as follows: the patients' SAS, SDS, NIHSS, and MMSE scores.

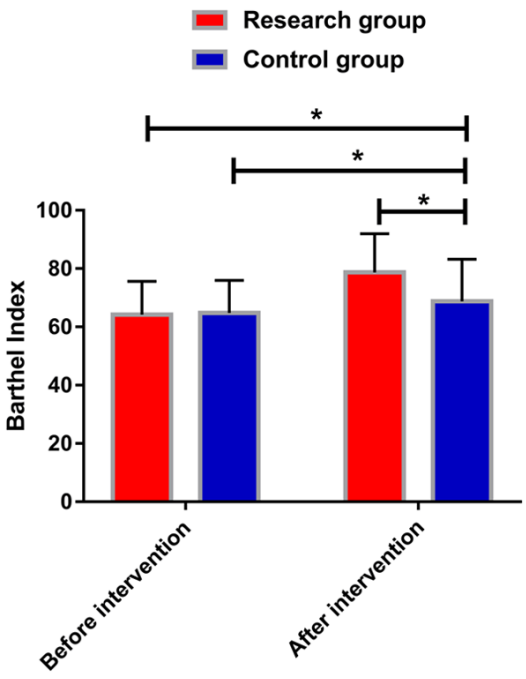

Figure 2. The Barthel index scores. After the treatment, the Barthel index scores in the RG increased and were higher than they were in the CG. Note: * indicates that there is a significant difference between the two groups ($P < 0.05$).

The secondary outcome measures were as follows: the Barthel index and the SF-36 scores.

Statistical methods

The data were statistically assessed using SPSS 20.0 (IBM Corp, Armonk, NY, the States), and the figures were drawn using GraphPad 7. The dose data distribution were analyzed using K-S tests, in which the normal parts were represented as mean ± standard deviation (means ± SD). The inter-group comparisons were assessed using independent-samples T tests, and the intra-group comparisons were done using paired T tests. The utilization rates of the count data were represented as (%) and then compared using chi-square tests and expressed as χ^2. $P < 0.05$ denotes that a difference is statistically significant.

Results

Baseline data

The patients' ages, BMI, history of smoking and drinking, places of residence, education levels, and disease types in the RG and the CG showed no significant differences ($P > 0.05$) (**Table 1**).

The SAS, SDS, NIHSS, and MMSE scores before and after the treatment

Both groups had no differences in their SAS, SDS, NIHSS, and MMSE scores before the treatment ($P > 0.05$). Compared with the CG, the SAS, SDS, and NIHSS scores in the RG were lower, but the MMSE scores were higher after the treatment ($P < 0.05$) (**Figure 1**).

Barthel index scores before and after the treatment

Both groups had no difference in their Barthel index scores before the treatment ($P > 0.05$), but the scores in the RG were higher than the scores in the CG after the treatment ($P < 0.05$) (**Figure 2**).

The SF-36 scores before and after the treatment

The patients' SF-36 scores were observed. It was found that the physical health (physiological function, physiological role, bodily pain, general health) and mental health (vitality, social function, emotional role) scores in the RG were higher than they were in the CG ($P < 0.05$) (**Figure 3**).

Discussion

The interaction between depression and stroke is very complicated. Post-stroke depression is the most common neuropsychiatric complication of stroke. The main pathogenesis is related to central nervous system injuries, endocrine system disorders, social influences, the psychological environment etc. after a stroke. When stroke patients have depression symptoms, the depression can increase the level of the neurological impairment and it can also increase the patients' feelings of pessimism, depression, decreased interest, irritability, cognitive dysfunction etc. Depression will also increase the morbidity, cause poor mortality and functional recovery, so it has many negative effects on the prognoses of stroke patients [16, 17].

Antidepressants, such as fluoxetine, can improve the prognosis of stroke and are widely used in the clinical treatment of post-stroke depression patients. This effect may go far beyond depression, such as exercise recovery. The main biological theory of fluoxetine is the

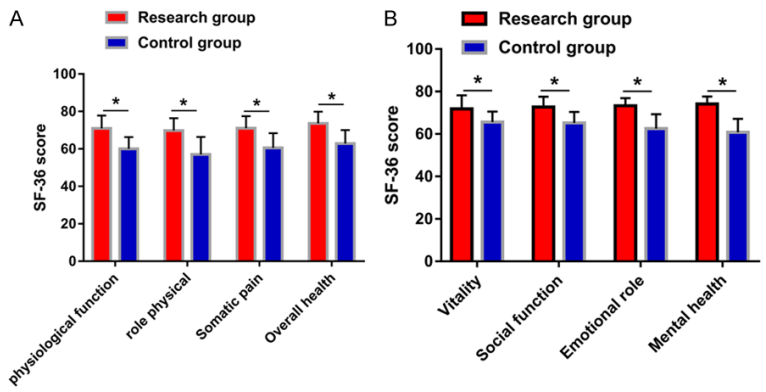

Figure 3. SF-36 score. A. The SF-36 scores of the patients in the RG after the treatment were higher than the SF-36 scores in the CG. B. The mental health scores of the SF-36 in the RG after the treatment were higher than the SF-36 mental health scores in the CG. Note: * indicates that there is a significant difference between both groups ($P < 0.05$).

amine hypothesis. It's conceivable that ischemic damage interferes with the upward projection of the midbrain and brainstem, resulting in a decrease in the bioavailability of biogenic amine-5-hydroxytryptamine (5HT), dopamine (DA), and norepinephrine (NE). Acetylcholine is also involved, and it can relieve patients' depression and promote the recovery of nerve function defects to a certain extent [18, 19]. In clinical practice, it has also found that there is still room for improvement in the efficacy of such antidepressants [20]. rTMS can improve motor ability after stroke by affecting the cortical excitability in relatively concentrated areas. Low-frequency rTMS in unaffected cerebral hemispheres may enhance motor ability by regulating the competition between cerebral hemispheres [21, 22]. Studies have shown that combining rTMS with antidepressants may improve the effectiveness of each treatment, especially in emotional regulation [23, 24].

In this research, post-stroke depression patients were treated with fluoxetine and fluoxetine combined with rTMS. We first compared the SAS, SDS and NIHSS scores of both groups to evaluate the patients' mental health and neurological function. The results showed that the patients who received fluoxetine combined with rTMS had better outcomes than those treated with just fluoxetine, which indicated that giving fluoxetine combined with rTMS can improve patients' psychological status, reduce their incidence of depression, and improve their neurological function. We further observed the MMSE and Barthel index scores and found that scores in the RG were higher than those in the CG. Finally, we observed the patients' SF-36 scores and found that the scores of the patients in the RG were higher than the scores in the CG. It may be due to the fact that rTMS can improve cerebral blood perfusion, decrease the density of adrenergic receptors in the cerebral cortex, weaken the sensitivity of the hypothalamic postsynaptic model 5-HT receptors, and then stimulate an increase in the dopamine neurotransmitter secretions in the hippocampus and striatum. Combined with the antidepressant effect of fluoxetine, the two treatments promote each other and further improve the depression levels of the patients [25, 26]. Furthermore, in the process of rTMS, high-frequency magnetic stimulation through the left prefrontal lobe can stimulate the cerebral cortex, the subcortical pathway, and the limbic system, thereby stimulating the excitement and improving the positive emotions and cognitive functions of the body. It also promotes the recovery of neurological function after further regulating patients' depression and cognitive functions.

We have preliminarily proved the value of fluoxetine combined with rTMS in post-stroke depression patients. But there are still have some limitations. For one thing, the study cohort was relatively homogeneous, so it is not ruled out that there may be differences in the outcomes among different races. For another, our study did not follow up the patients' prognoses. Hence, we'll conduct more experimental analysis in the future to enrich our results and provide services for clinical practice.

In general, fluoxetine combined with rTMS can effectively improve the psychological mood, cognitive function, and neurological function of post-stroke depression patients. Hence, it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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