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Effects of Intensive Exercise Training Combined with Prophylactic Antidepressant Treatment on Motor Function and Depression in Patients with Stroke

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Abstract: Objective： To observe the effects of intensive exercise training combined with prophylactic antidepressant treatment on motor function and depression in patients with stroke. **Methods：** 45 patients with stroke (not diagnosed as post stroke depression，PSD) were randomly divided into three groups by random number table: the simple treatment group, the intensive exercise training group, and the intensive exercise training + prophylactic antidepressant treatment group, each for 15 cases. The patients of 3 groups were given routine stroke drug therapy and rehabilitation training. On the basis of this, the intensive exercise training group increased motor function training once a day. In addition to increasing motor function training once a day, the intensive exercise training + prophylactic antidepressant treatment group was given further prevention of antidepressant medication. The modified Barthel index scale (MBI), Fugl-Meyer Assessment (FMA), Self-rating depression scale (SDS) were used to evaluate the motor function and depression of the patients in the 2rd and 4th week after treatment. **Results：** Before treatment, there was no significant difference among the three groups in Barhtel, FMA and depression index. After treatment, the Barthel index and FMA score of the treatment group and the intensive exercise training + prophylactic antidepressant treatment group were significantly different from those of simple treatment group. The ADL and FMA scores of the 2 groups were higher than those of the simple treatment group（$P < 0.05$）. Compared with the intensive exercise training group, the Barthel index and FMA score showed no significant advantage in the intensive exercise training + prophylactic antidepressant treatment group. The SDS scores of the three groups were not statistically significant between the groups before and after treatment (in the group). **Conclusion：** Intensive exercise training therapy can effectively improve the overall prognosis of patients with stroke and improve the effects of clinical rehabilitation. There was no statistically significant difference in the recovery of motor function and the incidence of PSD in patients receiving prophylactic antidepressant treatment compared with patients who did not receive prophylactic antidepressant treatment. Considering that there is no PSD in the patients before and after the experiment, and the observation time is short, it is still not possible to draw the conclusion that prophylactic antidepressant treatment is ineffective.

Keywords: PSD, intensive exercise training, modified Barthel index scale (MBI), Fugl-Meyer Assessment scale (FMA), depression, prophylactic antidepressant treatment

Introduction

In recent years, with the increased incidence of stroke [1], the decline of mortality and the onset of a younger age, the proportion of people who left limb and mental disorders after stroke is increasing year by year. Not only does it cause serious damage to the patient's motor ability, but also leads to a variety of complications, resulting in increased disability and declined quality of life, such as long-term bed pressure sores, falling pneumonia and lower extremity deep vein thrombosis, which have had a more mature means of coping in the treatment and nursing of stroke[2]. However, the psychological problems of patients with stroke is a severe test that we need to face. PSD is one of the most common psychological disorders in patients with stroke, which will seriously affect the patient's willingness to

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recover and reduce the effect of rehabilitation therapy [3]. If the clinical diagnosis and treatment is not timely, it will delay the time of rehabilitation treatment and cause damage to the prognosis of patients. When the field of neural repair has not yet made a breakthrough currently, there is an urgent need for more efficient, more comprehensive, more timely rehabilitation intervention, to maximize the improvement of the patient's ability to exercise and improve the physical quality. The purpose of this study was to investigate the effects of intensive training combined with prophylactic antidepressant therapy on the prognosis of stroke. 45 cases of patients with stroke in our hospital were selected, and the results are reported as follows.

1 Materials and methods

1.1 General information

The patients with stroke in rehabilitation department of Huangdao Hospital Affiliated to Qiingdao University from May 2015 to October 2016 were selected as the objects of study. The patients were all at their first onset. Inclusion Criteria： 1. In accordance with the diagnostic criteria of cerebrovascular disease in the Fourth National Conference on cerebrovascular diseases; 2. All patients are diagnosed as cerebral hemorrhage or cerebral infarction by MRI and CT and the course of disease was not more than 6 months and the disease is in a stable phase；3. Aged from 18 to 80; 4. No severe cognitive impairment and the score of MMSE >20；5. No serious manifestations of aphasia, be able to understand, answer questions correctly, and cooperate with the inspection; 6. (before and after the onset) No history of psychiatric symptoms and no history of psychotropic drugs; 7. The score of SDS <53. Exclusion criteria：1. Drug allergy；2. Worsening of the disease, such as new infarction, intracranial hemorrhage, and pulmonary embolism;3. Severe organic diseases, such as liver and kidney disease, heart failure, malignant tumor, respiratory failure, arthritis, abnormal growth and development；4. Poor compliance, unable to accurately perform the doctor's advice；6. Interruption of the treatment.

In this study, the patients were randomly divided into three groups by random number table: the simple treatment group, the intensive exercise training group, and the intensive exercise training + prophylactic antidepressant treatment group. After the chi square test, there was no significant difference between groups in sex distribution（X2=0.194，P=0.908，P>0.05）；There was no significant difference in age and course of disease between the groups after the simple factor analysis of variance（P>0.05，See Table 1）. In summary, the general data between groups were comparable.

Table 1. Comparison of basic data between groups

	Number of cases	Sex		Age	Type of Stroke		Course of disease
		Male	Female		Cerebral hemorrhage	Cerebral infarction	
Simple group	15	9（60.0%）	6（40.0%）	58.33±9.72	8（53.3%）	7（46.7%）	113.20±33.54
intensive exercise training group	15	10（66.7%）	5（33.3%）	58.07±8.42	5（33.3%）	10（66.7%）	110.20±33.69
intensive exercise training + prophylactic antidepressant treatment group	15	10（66.7%）	5（33.3%）	57.80±10.44	9（60.0%）	6（40.0%）	122.27±39.84
F value/X^2 value		0.194		0.012	2.312		0.462
P value		0.908		0.988	0.315		0.633

1.2 Therapeutic method

Three groups were given conventional treatment. Drugs were given for the control of blood pressure, blood sugar and lipid, as well as the nutrition of nerves, and improving blood supply to the brain.

（1）Routine rehabilitation training：① The subjects were given acupuncture, physical therapy (intermediate frequency electrical stimulation, EMG biofeedback, functional electrical stimulation) and other interventions；② Rehabilitation training is based on Brunnstrom and Bobath technology, mainly for the development of neural therapy, including the good limb position, maintenance of joint mobility, joint mobilization techniques, strength training, balance function training, sitting balance, sit to stand

training, walking training etc. , which can enhance the muscle strength and muscle endurance, improve the patient's ability to coordinate. Once a day, every time for 50min, 5d per week, continuous training for 4 weeks.

（2）The simple group only carried out the routine rehabilitation training. On the basis of this, the rehabilitation training once a day was added in the intensive training group. The time and content of training were the same as above. In addition to the additional rehabilitation training once a day, the intensive exercise training + prophylactic antidepressant treatment group was given the reuptake inhibitor of 5-HT, Sertraline Hydrochloride Tablets (Zoloft) for 50mg/d, to prevent the PSD, lasting for 4 weeks.

1.3 Evaluation method

The efficacy of subjects were evaluated by the same physician before treatment, at the 2rd week and 4th week. The specific assessment included the following three aspects:

(1) MBI

MBI is one of the most common scales used for the evaluation of assess daily living (ADL). It includes eating, bathing, modification (washing, brushing, shaving, hair), dressing, stool control, urine control, toilet, bed chair transfer, walking (wheelchair), up and down the stairs. Each item was fractionized from 1 to 5 level, that is, complete dependence, maximum help, medium help, minimal help and complete independence. A total score of 100 means completely normal. The score more than 60 means basic self-care. The score ranging from 60 to 40 means moderate disability, needing help in life. The score ranging from 40 to 20 means severe disability, with an obvious life dependence. The score less than 20 means total disability, with a completely dependent life.

(2) FMA

The FMA is a quantitative evaluation of the motor function, joint mobility, balance function and sensation of the limbs, to assess the severity of stroke patients with hemiplegia. It includes the upper limb (a total of 33 items, the highest single score of 2 points) and lower limbs (17 items, the highest single score of 2), with a total score of 100 points. The overall condition of the patients is more comprehensive. A total score of 100 means normal motor function. The score less than 50 is level I, which means severe limb dysfunction. The score ranging from 50 to 84 is level II, which means obvious dyskinesia. The score ranging from 85 to 95 is level III, which means moderate dyskinesia. The score ranging from 96 to 99 is level IV, which means mild dyskinesia.

3) SDS

SDS scale is one of the most common measurement tools for clinical depression. It is simple and convenient, and has low requirements for the raters, which can be used as a clinical examination catalog. SDS includes 20 items, the degree of dependence is divided into 4 levels. The cutoff value of SDS scale is 53. The score ranging from 53 to 62 is mild depression；The score ranging from 63 to 72 is moderate depression. The score more than 72 is severe depression. Although the clinical Hamilton Depression Scale (HAMD) is the most common rating scale for depression, it has good reliability and validity. However, it is difficult for the raters to hold professional qualifications [3]. Therefore, it is not adopted.

1.4 Statistical method

The results of clinical observation of patients in three groups were studied. The SPSS 22.0 software was used for statistical analysis and processing. The measurement _data obeyed normal distribution, expressed by $\bar{X} \pm S$. It was expressed by the median (four percentile) when not obeyed the normal distribution. The measurement data was expressed by number of cases (percent). The comparison of age and the course of disease between groups were analyzed by one-way ANOVA. The chi square test was used to compare the sex distribution between groups. The repeated measure ANOVA and one-way ANOVA were used to compare the scores of Barthel, Fugl-Meyer and SDS between groups. The pairwise comparison between groups was compared by LSD method. Taking a=0.05 as the inspection level，if $P < 0.05$, the difference is statistically significant.

2 Results

2.1 Comparison of the ability of daily living (Barthel score) in group and between groups

There was no significant difference in Barthel score in the three groups before and after treatment （F=0.163，P=0.850，P>0.05）.

Comparison in group：The pairwise comparison was used before and after treatment. Comparing the results 2 weeks after treatment with that before treatment, there was no significant difference in the scores of simple treatment group. There were significant differences in the scores of the intensive training group and intensive exercise training + prophylactic antidepressant treatment group. Comparing the results 4 weeks after treatment with that 2 weeks after treatment, there were significant differences in Barthel score of the three groups.

Comparison between groups ： After repeated measures analysis of variance, after 2 weeks of treatment, the changes of scores of the intensive training group and the intensive training + preventive antidepressant treatment group were higher than those of the simple treatment group. There was no significant difference in the changes of scores between the intensive training group and the

intensive training + preventive antidepressant treatment group. After 4 weeks of treatment, the changes of scores of the intensive training group and the intensive training + preventive antidepressant treatment group were higher than those of the simple treatment group. There was no significant difference in the changes of scores between the intensive training group and the intensive training + preventive antidepressant treatment group.

Table 2. Comparison of Barthel scores in group and between groups ($\bar{X} \pm S$)

	simple treatment group	intensive exercise training group	intensive exercise training + prophylactic antidepressant treatment group	F value	P value
Before treatment	36.00±12.89[a]	37.67±12.44[a]	35.13±11.66[a]	0.163	0.850
2 weeks after treatment	36.40±10.29[a]	47.60±10.32[b]	48.07±9.15[b]	6.632	0.003
4 weeks after treatment	43.33±12.49[c]	53.73±10.97[d]	51.87±9.41[d]	3.792	0.031
F value	33.374	70.698	24.988		
P value	<0.001	<0.001	<0.001		

Remarks：Right superscript contained the same letter meant there was no significant difference between groups（P>0.05）while not contained the same letter meant there was a significant difference between groups（P<0.05）.

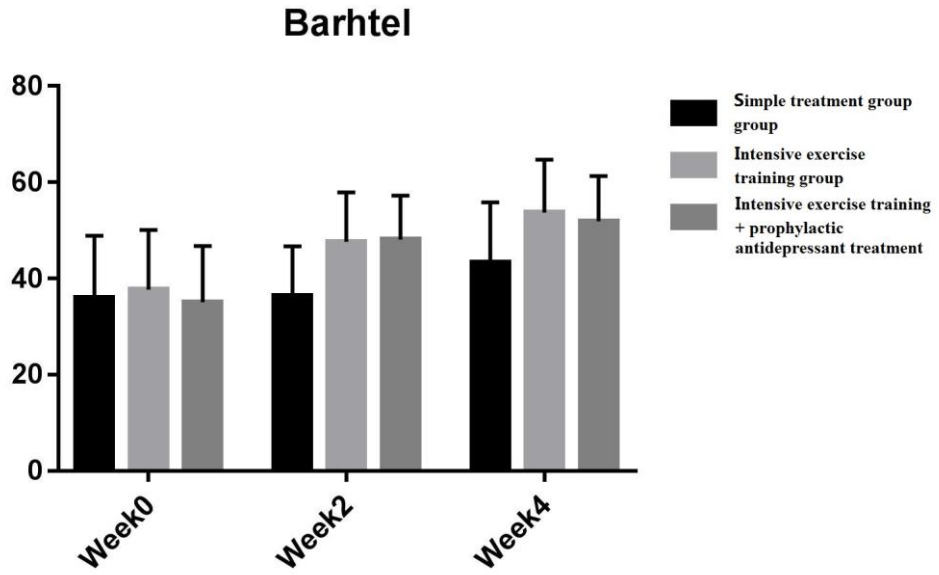

Figure 1.

2.2 Comparison of motor function (Fugl-Meyer score) in group and between groups

After one-way ANOVA, there was no significant difference in Fugl-Meyer score in the three groups before treatment（F=0.133，P=0.876，P>0.05）.

Comparison in group：The pairwise comparison was used before and after treatment. Comparing the results 2 weeks after treatment with that before treatment, there was no significant difference in the scores of three groups. Comparing the results 4 weeks after treatment with that 2 weeks after treatment, there were significant differences in the scores of three groups.

Comparison between groups：After repeated measures analysis of variance, after 2 weeks of treatment, the changes of scores of the intensive training group and the intensive training + preventive antidepressant treatment group were higher than those of the simple treatment group. There was no significant difference in the changes of scores between the intensive training group and the intensive training + preventive antidepressant treatment group. After 4 weeks of treatment, the changes of scores of the intensive training group and the intensive training + preventive antidepressant treatment group were higher than those of the simple treatment group. There was no significant difference

in the changes of scores between the intensive training group and the intensive training + preventive antidepressant treatment group. （P>0.05）

Table 3. Comparison of Fugl-Meyer scores in group and between groups ($\bar{X} \pm S$)

	simple treatment group	intensive exercise training group	intensive exercise training + prophylactic antidepressant treatment group	F value	P value
Before treatment	36.07±13.33[a]	36.20±12.76[a]	34.20±9.09[a]	0.133	0.876
2 weeks after treatment	42.67±12.15[b]	52.80±7.72[c]	50.07±7.26[c]	4.759	0.014
4 weeks after treatment	49.13±14.05[d]	59.47±7.46[e]	57.73±6.45[e]	4.678	0.015
F value	59.876	42.602	48.393		
P value	<0.001	<0.001	<0.001		

Remarks：Right superscript contained the same letter meant there was no significant difference between groups （P>0.05）while not contained the same letter meant there was a significant difference between groups（P<0.05）.

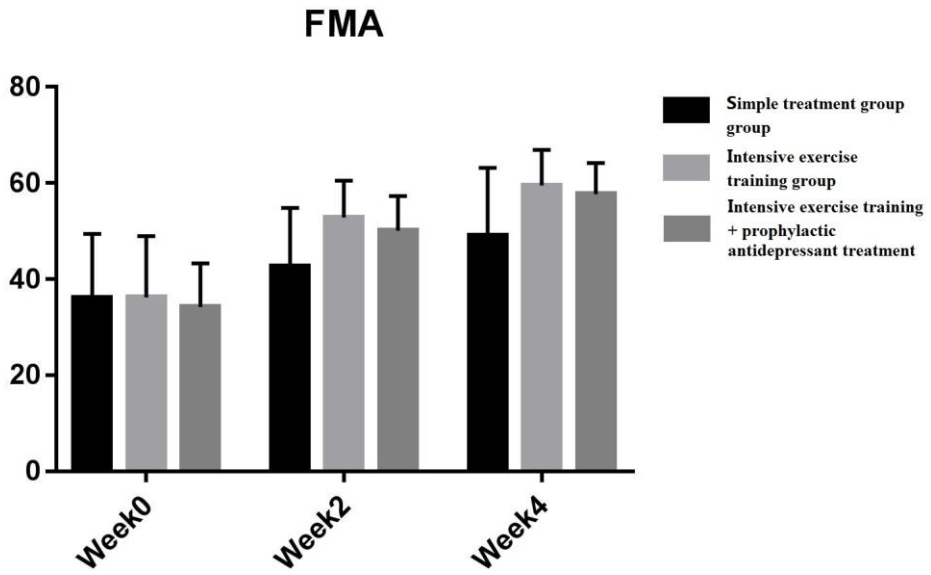

Figure2.

2.3 Comparison of SDS scores in group and between groups

The patients of 3 groups has no history of depression, and the SDS scores before treatment were not up to the diagnostic criteria for depression（SDS< 53 分）; After one-way ANOVA , there was no significant difference in SDS score of the three groups before and after treatment（F=0.287，P=0.752，P>0.05）.

Comparison in group：The pairwise comparison was used before and after treatment. Comparing the results 2 weeks after treatment with that before treatment, there was no significant difference in the SDS scores of three groups（P>0.05）. Comparing the results 2 weeks after treatment with that 4 weeks after treatment, there was no significant difference in the SDS scores of three groups（P>0.05）. Comparing the results before treatment with that 4 weeks after treatment, there was no difference in the SDS scores of three groups（F=0.635，P=0.532）.

Comparison between groups ： After repeated measures analysis of variance, the patients of three groups before treatment and after treatment for 2 weeks, after treatment for 2 weeks and after treatment for 4 weeks, the change of SDS score was not statistically significant（F time*group=610，P=0.657，P>0.05）. There was no significant difference in SDS score of the three groups in different treatment time （P>0.05，see Table 4）.

Table 4. Comparison of SDS scores between groups ($\bar{X} \pm S$)

	simple treatment group	intensive exercise training group	intensive exercise training + prophylactic antidepressant treatment group	F value	P value
Before treatment	26.13±5.76	25.87±6.08	24.53±6.73	0.287	0.752
2 weeks after treatment	26.73±5.09	25.67±5.88	24.67±6.38	0.475	0.625
4 weeks after treatment	26.47±5.46	26.33±5.44	24.67±6.44	0.449	0.641
F value	1.358	0.467	0.211		
P value	0.274	0.631	0.811		

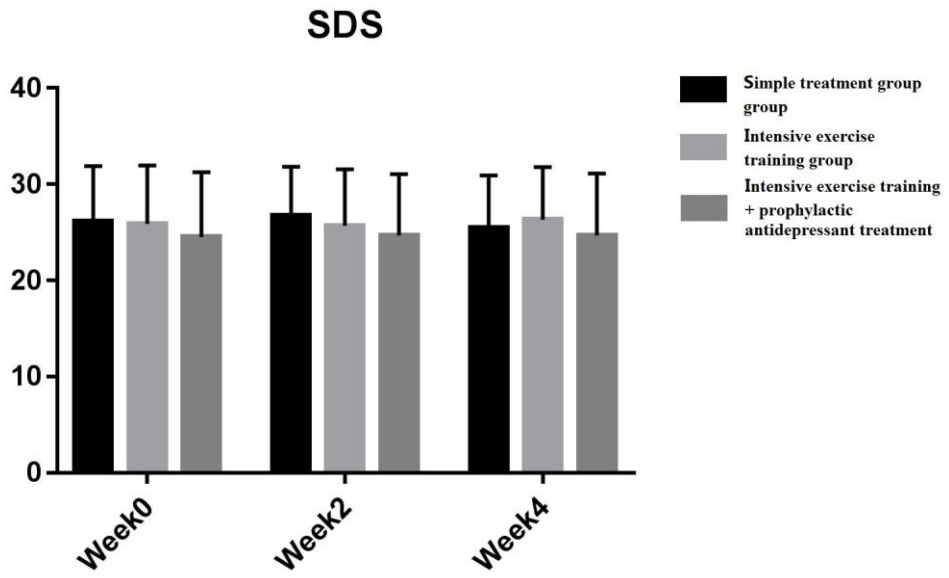

Figure 3.

3 Discussion

3.1 Intensive training

Motor dysfunction is one of the common sequelae of stroke. The recovery of motor function is the primary objective for most patients. The improvement of motor function can directly improve the self-care ability of patients and improve the quality of life of patients. Intensive training is an effective intervention in early stage of stroke. At present, it has been proved that intensive training can improve the recovery of motor function of patients with stroke [14]. The possible mechanisms include brain plasticity. In the case of the damage of central nervous system, the brain function in the normal physiological state is limited. However, by increasing the training time, the number of times, the repeated training can promote the function of the brain, improve the efficacy of synaptic nerve conduction pathway [15], and accelerate the compensatory process of re innervation; Another mechanism is brain derived neurotrophic factor (BDNF); The BDNF [16] is a protein synthesized in the brain, which is widely distributed in the central nervous system and plays a protective role in the neuronal cells. The related results have showed that the higher the level of serum BDNF is, the lighter the symptoms of depression will be (1). Heyman et al. [17] found that the level of BDNF in normal human body increases with the increase of exercise load, which provides the theoretical basis for strengthening the training of anti-depression symptoms.

On the basis of the routine rehabilitation training, this study further increased the amount of training. The results showed that the Barthel and FMA scores of the intensive training group, the intensive exercise training + prophylactic antidepressant treatment group were better than those of the simple treatment group. It is proved again that the repetition of training and the increase of training time are helpful to improve the ability of daily living and motor function of hemiplegic patients after stroke. There was no

significant difference in the Barthel score of the simple treatment group before and after treatment for 2 weeks. Comparing the results 2 weeks after treatment with that 4 weeks after treatment, there was a significant difference. The difference of Barthel score and FMA score in the intensive training group and the intensive exercise training + prophylactic antidepressant treatment group was significantly higher than that of the simple treatment group after treatment for 2 weeks. Moreover, after 4 weeks of treatment, the scores of the intensive training group and the intensive exercise training + prophylactic antidepressant treatment group were significantly higher than those of the simple treatment group. On the basis of improving the ability of daily living and motor function of hemiplegic patients after stroke, the intensive exercise training can improve the ability of daily living and motor function within a short time after treatment, which meets the requirements of early rehabilitation treatment.

The study showed that there was no significant difference in the Barthel and FMA scores between the intensive training group and the intensive exercise training + prophylactic antidepressant treatment group in different period. It cannot come to the conclusion that the intensive training combined with prophylactic antidepressant therapy has advantage over the intensive training in the improvement of patients' daily living ability and motor function. The core idea of prophylactic antidepressant therapy is to reduce the risk of developing new PSD in patients with stroke, so as to improve the effect of rehabilitation training；In this study, three groups of patients were not diagnosed with depression before treatment, there was no significant difference in SDS score of the three groups before and after treatment （P>0.05）. In the course of treatment, the three groups did not appear new PSD patients. Therefore, there was no difference of comparison of conditions in the three groups during the treatment, so that the efficacy of the intensive training combined with prophylactic antidepressant therapy cannot be evaluated. The results of this study can only show that in the time period of the treatment, in the selected 45 non PSD patients with stroke, there was no significant difference in the improvement of daily life ability and motor function after comparing the intensive training combined with prophylactic anti-depression therapy with the simple treatment. It cannot conclude that the prophylactic antidepressant treatment of stroke patients has no effects on the improvement of daily living ability and motor function. The next step is to extend the duration of the trial and expand the sample size to further investigate whether antidepressant treatment can reduce the incidence of PSD, and whether there is a difference in the improvement of motor function in patients with the intensive training combined with prophylactic anti-depression therapy after compared with the intensive training.

3.2 Prophylactic antidepressant treatment

With the decline of the age of onset of stroke [4], the aging of the population and the improvement of medical conditions, the proportion of patients with limb dysfunction and neurological impairment after stroke in China increased year by year, which not only causes a lot of valuable labor loss, but also long-term medical investment even causes the waste of medical resources. Early rehabilitation therapy can effectively improve the prognosis of patients, improve self-care ability, establish self-confidence, prevent the occurrence of complications, and effectively reduce the mortality and disability rate after stroke [5]. As the most effective treatment method, the early rehabilitation training has been widely recognized by the medical profession. Therefore, it is a common problem in the field of rehabilitation medicine to explore more effective rehabilitation training mode and to eliminate the negative factors that affect the treatment.

PSD (PSD) is one of the most common complications after stroke, which is one of the important factors affecting the rehabilitation of patients with stroke. It is mainly manifested as insomnia, mental fatigue, irritability, energy loss, and emotional loss and so on. On the basis of this, some of the patients with severe post-stroke depression developed further anxiety, anorexia, weight loss, distraction, loss of interest, and even suicidal tendencies [6]. PSD can cause severe emotional disorders, reduce the willingness of patients to accept treatment voluntarily, and delay the golden period of early treatment (3 months after onset) [7], which affects the effects of rehabilitation intervention. Related reports indicate that the course of stroke is related to the incidence of PSD. The incidence of PSD in China accounts for about 1/3 of patients with stroke (27.3%-49.7%). Most of them occurred within 1 year after stroke. Even in the 1~5 years after the onset of stroke, there are still 18%~30% of patients with varying degrees of depressive symptoms [8].

On the other hand, studies have shown that PSD is closely related to the severity of stroke. The higher the degree of physical disorder, the higher the incidence of PSD；Although the physical disorder cannot directly lead to depression, but the damage of the nerve function will be further induced, aggravating the degree of depression [9]. As the PSD affects the patient's psychological state and hinder the progress of rehabilitation therapy, at the same time, the limb disorders and neurological deficits will also cause an increase in the degree of depression, leading to the formation of a negative cycle. The rate of missed diagnosis of PSD is higher clinically [10], which cannot be timely diagnosed and treated. It takes a long time to take antidepressant drugs, which

usually takes 2~4 weeks to achieve satisfactory results [11], seriously affecting the treatment of patients with stroke in the golden age; In theory, prophylactic antidepressant therapy should have a positive effect on the rehabilitation of patients with stroke and the prevention and treatment of depression.

This experiment was designed to observe the preventive effect of antidepressant drugs on depression in stroke patients with undiagnosed depression. The results showed that there were no significant differences in SDS scores in group and between groups the before treatment, after treatment for 2 weeks and after treatment for 4 weeks. There were no new cases of PSD before and after treatment in 15 subjects of the intensive exercise training + prophylactic antidepressant treatment group. However, on the premise of not receiving antidepressant treatment, the other 2 groups (the simple treatment group, the intensive training group), there were no new cases of PSD before and after the treatment. The results was not consistent with the expected effects of treatment, and the incidence of PSD in the experimental group was obviously lower than that of most literatures. Several possible reasons are as follows: ① Most of the studies on the incidence of PSD are based on clinical follow-up studies. The source of the patients in this study were hospitalized stroke patients, the composition of the two groups were different. ② Patients who had previously had a history of depression and those with post-stroke depression were excluded in the trial. The results were affected by selection bias. ③ In order to ensure the maximum extent to ensure that the patients can listen to the training instructions, understand and answer the content of the depression scale and other factors, the patients with serious aphasia were excluded. Foreign individual literature has taken the aphasia as an independent risk factor for PSD. Wang Huiting [12] et al., in the study of 'the status quo and influencing factors of depression in elderly patients with stroke', it is concluded that speech function is the main influencing factor of PSD in elderly patients （$P<0.05$）, and there is a positive correlation between speech function and depression in elderly patients with stroke （$r=0.224, P=0.009$）. It is suggested that aphasia plays a major role in PSD. ④ The observation time was short, and it was difficult to observe the change of PSD in 1 month. According to the Astrom's [13] follow up study of 98 acute stroke patients over a period of 3 years, the incidence of acute PSD was 25%. By the end of 3 months, it was decreased to 31%. It was decreased to 16% after 1 year, but it was increased to 29% after 3 years. It is believed that the incidence of depression in patients with stroke will fluctuate significantly with the change of duration of the disease. The incidence of depression at specific time points cannot represent the overall incidence of PSD in the course of treatment; ⑤ Comparing the SDS with the HAMD performed by psychiatric professionals, both the process and the accuracy of results will be relatively low. Patients with severe depression may be diagnosed, and patients with mild depressive symptoms can not reflect the subtle changes of psychological state, which may result in the fact that there was no difference between the three groups before and after treatment with SDS. ⑥ The onset time of most antidepressants is 2~4 weeks after treatment [11]. Although this trial period included this period of time，it means that a part of patients in antidepressant treatment group may take effect in the fourth week. Under the premise that three groups of patients did not appear new PSD cases, the efficacy of antidepressant drugs cannot be evaluated. Currently, the antidepressant drugs are commonly used in the treatment of PSD. Various types of literature hold positive views on the effects of treatment. However, it is not clear that the use of antidepressant drugs in the prevention of PSD after stroke; In view of the high incidence of PSD, the adverse effects of PSD on early rehabilitation and the time window of antidepressant treatment [18], the prophylactic antidepressant treatment is theoretically meaningful. In the past, a large number of studies were based on the clinical diagnosis of PSD patients, and this study is not comparable. The results of this study failed to conclude that the prophylactic antidepressant treatment has inhibitory effects on the incidence of PSD in patients with stroke. However, it is still not able to conclude that prophylactic antidepressant treatment is positive or negative. In this experiment, 45 patients in the process of treatment did not appear PSD. The next step is to extend the observation time, expand the sample size, relax the selection criteria and avoid bias, in order to get more accurate conclusions.

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