Effect of Acupoint Stimulation Combined with Traditional Chinese Medicine on Behavioral and Neurotransmitter Levels in Rats with Post Stroke Depression

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Abstract: Post stroke depression (PSD) is a secondary depressive symptom after stroke, which has a significant negative impact on the quality of life and rehabilitation outcomes of patients. However, there is currently no effective treatment method. Our preliminary clinical research group believes that the main pathogenesis of PSD is "yang qi stagnation", and the treatment principle is "warming yang to relieve depression". The animal experiment study found that Tongdu Yishen acupuncture combined with Wushen Decoction could effectively improve the depressive symptoms of PSD rats, which was mainly manifested in: significantly reducing the Zea Longa Neuroethology score of PSD rats, and significantly increasing the percentage of sucrose water consumption, open box experiment horizontal exercise and open box experiment vertical exercise scores, and significantly increasing the content of 5-HT and Brain-derived neurotrophic factor (BDNF) in the serum of PSD rats.

Keywords: post stroke depression, acupuncture, traditional Chinese medicine, behavioral studies

1. Introduction

Post stroke depression (PSD) is a report of mental and emotional disorders based on the occurrence of cerebrovascular disorders, with a cumulative incidence of 55%. PSD patients can experience depression or somatization symptoms caused by depression, and even suicidal psychology, which not only increases their mental pain but also seriously affects their social function. PSD brings a heavy burden to families and society, and is also related to the increase in mortality rate of stroke patients [1,2]. Despite the significant negative impact of the effect, there is currently no good treatment method. Therefore, it is urgent to find effective methods for treating PSD, which can improve the quality of life and rehabilitation of patients. PSD is the most common mental illness. PSD is closely related to physical movement and cognitive function, prognosis recovery, and further deterioration of quality of life. In addition, depression can also have a negative impact on patients' initiative in rehabilitation treatment [3]. Therefore, there is a bidirectional relationship between depression and stroke, with stroke leading to an increase. The risk of biological PSD, but depression is also an independent risk factor for stroke and stroke mortality. The pathophysiological mechanisms of PSD are not fully understood, and biological, behavioral, and social factors are believed to be related to it. Therefore, PSD is a multifactorial process [4]. Biological factors can be attributed to several different factors: stroke location, stroke type, involved neurobiological pathways, inflammation and apoptosis mechanisms, and genetic factors. At present, PSD is mainly treated by drugs, such as Monoamine oxidase inhibitor (MAOI), cyclic antidepressants and some new antidepressants [5]. Acupuncture and moxibustion and traditional Chinese medicine have significant effects on depression [6]. This study explored the possible mechanism of treating post-stroke depression by observing the effect of acupoint stimulation combined with traditional Chinese medicine on the behavior and neurotransmitter levels of post-stroke depression model rats.

2. Experimental materials and methods

2.1 Experimental animals

The Laboratory rat in this experiment were all from the Experimental Animal Center of Binzhou Medical University. Variety: Sprague Dawley (SD) rats, weighing 250-300g, male, classified as clean. All rats were raised in the SPF animal feeding room by professionals. 4-5 rats in each cage were raised at room temperature of 18-24 °C, relative humidity of 40-60%, natural ventilation and light, and feed and drinking water were supplemented for rats in time. All animals were raised adaptively for one week and used for experiments. The animals and operations were tested in accordance with the principles of the Ethics Committee of the Medical Experimental Animal Center of Binzhou Medical University.

2.2 Sample size estimation

According to the general estimation method for the sample size of experimental animals and the opinions of experts in basic research, the sample size of each group of rats should be around 6-8, and if the sample size of each group is ≥ 6 rats, statistical analysis can be conducted. Considering the mortality rate of rat modeling and other factors, a preliminary sample size of 12 per group is proposed. There are a total of 48 animals in 4 groups.

2.3 Model establishment

(1)Stroke modeling methods

A rat MCAO model (focal cerebral ischemia rat model on the right side) was established using the thread occlusion method established by Koizumi et al [7-8]. The steps are as follows: ① SD rats were anesthetized by intraperitoneal injection of 10% Chloral hydrate at a dose of 1g/kg body weight; ② Lie the anesthetized rat's limbs on their backs and fix them on the operating table, and pull out the rat's tongue slightly outwards; ③ Cut off the hair from the anterior neck area of the rat, fully expose the skin, and wipe the skin with iodine; ④ Cut the skin in the middle of the neck for about 2 cm, passively separate the nerves, blood vessels and muscle connective tissue, fully expose the right common carotid artery (CCA), external carotid artery (ECA) and internal carotid artery (ICA), and avoid excessive traction during the separation process to avoid damaging the Vagus nerve. Ligate the proximal common carotid artery, ligate the ECA near the bifurcation, and temporarily clamp the ICA. At the proximal end of the CCA where it is ligated, make a small incision at a 45 ° angle (do not cut off the blood vessels). Slowly insert the thread plug along this small incision through CCA and enter the middle cerebral artery through ICA, with an insertion depth of about 18 ± 1.5mm. Stop inserting the thread when resistance is obvious. At this point, the thread plug will block the blood flow of the middle cerebral artery (MCA), and finally ligate the insertion point; ⑤ Finally, the skin of the rats was sutured layer by layer, with an external thread plug of about 1cm left. The surgical area was disinfected, and 40000 units of penicillin were injected intraperitoneally after the surgery to prevent infection. The rats were placed on their backs in a cage filled with clean padding. ⑥ After 2 hours of ischemia in rats, slowly remove the thread plug, tighten the incision, and release the common carotid artery clamp or suture. ⑦ After waking up under anesthesia, the animal may experience unstable standing, weakness in the opposite limb, or turning to one side or crawling to the opposite side when lifting its tail, which serves as a criterion for the success of the model.

(2)PSD rat modeling method

After MCAO surgery, rats with 1-3 scores were scored for neurological function. On the third day after the first step of modeling, chronic unpredictable stress depression (CUMS) combined with solitary confinement method was used to create a PSD model. Raise rats in a single cage, that is, one per cage. A total of 9 stimuli were administered, and 1 stimulus was randomly administered daily for a total of 18 days, with each stimulus being administered for 2 days. Rats were subjected to unpredictable mild stress stimulation alternately every day for a total of 3 weeks to avoid tolerance to single stress of the same intensity. The 9 stimulation methods are as follows: ① fasting and water deprivation for 20 hours: cutting off material for 20 hours, cutting off water for 20 hours; ② Prohibition of drinking water for 17 hours: refers to the prohibition of drinking water for 17 hours; ③ Tilt the squirrel cage (45°) for 17 hours: Raise the cage to a 45 ° tilt angle with the ground, lasting for 17 hours; ④

Continuous illumination for 17 hours: At night, turn on the fluorescent lamp and continue illumination for 17 hours. ⑤ Wet cage for 21h: Add 200ml of water to every 100g of sawdust, causing the padding to become damp for 21h. ⑥ Swimming at 4 ℃ for 5 minutes: Place the animal in a bucket of ice water with a depth of approximately 20cm and a temperature of 4 ℃ (the water depth exceeds the height of the rat's tail touching the bottom). After 5 minutes, remove the animal and place it back in the cage. ⑦ Horizontal shaking for 5min: put the animals in the cage and place them on the horizontal Flatbed trolley, and push the Flatbed trolley forward and backward with moderate force. ⑧ Behavior restriction for 2 hours: Place the animal in a mineral water bottle (with the bottom cut off), remove the bottle cap, fix the bottom with tape, and return it to the cage after 5 minutes. ⑨ Clamp the tail for 1 minute: Use a wooden clip with a circular hole to clamp the tail of the rat for 1 minute (about 1cm away from the root and not too tight to cause ischemic necrosis of the tail);

2.4 Experimental animal grouping and intervention methods

The experiment was divided into four groups: Sham surgery group, model group, acupuncture group, acupuncture and medicine group.

①Sham surgery group: rats were subjected to model making operation without ligation. After suturing, feed normally without any treatment.

②Model group: only modeling without any treatment.

③Acupuncture group: the treatment group started treatment on the 21st day of modeling, and selected the acupoints of rats according to the animal acupoint atlas of Experimental acupuncture and moxibustion and Moxibustion.

One Needle Three Acupoints Method: Inject the needle from Shenting Point, stick it to the bone and stab it through Fenghui Point to Baihui Point.

Ghost Sect Thirteen Needles: Take the acupoints of Ren Zhong and Cheng Jiang and prick them without leaving any needles. Stab into the cheek car acupoint and the upper star acupoint along the way.

Xingnao Kaiqiao Needle: Take Wei Zhong, Chi Ze, Ji Quan, Neiguan, and San Yin Jiao, and use the method of lifting, inserting, and reducing.

Tongdu Wenyang Needle: Take the acupoints of the Du meridian and use the lifting and inserting method.

Leave the needle for 15 minutes after injection. Treat once a day for 8 consecutive weeks.

④ Acupuncture and medication group: Combination of medication group and acupuncture group.

2.5 Evaluation indicators

(1) Zea Longa method

The Zea Longa method is based on a 5-level 0-4 scale: 0- nerve injury; 1 point - contralateral forelimb adduction and flexion during tail lifting (mild nerve injury); 2 points - Rotation to the opposite side during crawling (moderate nerve damage); 3 points - When standing or crawling, tilting towards the opposite side (severe nerve injury); 4 points --- main activity with Disorders of consciousness.

(2) Sugar preference experiment

After fasting for 24 hours, calculate the amount of 1% sucrose solution for each Laboratory rat to drink for 24 hours, and determine the proportion of sugar water to drink for 24 hours. Method: After 24 hours of fasting and water deprivation, each group of animals was allowed to drink two different types of water: one bottle: tap water containing 1% sucrose, and the other bottle: tap water. At the 12th hour, the positions of the two water bottles were changed to eliminate the possible drinking habits of rats; By weighing animal drinking bottles, the 24-hour consumption of sucrose water and tap water can be obtained. And the sucrose preference was used as the evaluation standard to compare the changes in sucrose preference of each group of animals before and after the experiment. Sucrose preference%=sucrose water consumption/(tap water consumption+sucrose water consumption) x 100% Δ.

(3) Open box experiment

Rats exhibit exploratory behavior and emotional responses in unfamiliar, open, and potentially dangerous environments. The main manifestation is that after entering the open box, there are stress reactions such as standing, facial cleansing, defecation, and sniffing while walking. The horizontal score mainly reflects the activity level of rats, while the vertical score indicates the curiosity level of rats towards the new environment. The open box used in this experiment is a self-made wooden uncovered box. The perimeter is black with a white background, and the bottom is divided into 25 blocks of equal area. The horizontal activity score is based on the number of blocks crossed by animals (four legged entry), and the vertical activity score is based on the number of upright movements (two feet moving vertically away from the bottom). The laboratory is equipped with natural light and indoor sound insulation. Place one rat in the center square area each time, and then observe the number of times the rat travels between the squares and raises its front paws. A high-definition camera is placed on the top of the wilderness experiment reaction box to ensure coverage over the entire box. Place the Laboratory rat in the square in the center, click the automatic camera and timing button, and record the horizontal and vertical movement data of the rat respectively. Each rat was tested once, with a duration of 5 minutes. Record the number of horizontal movements, vertical movements, and fecal particles of the lateral major rats. Two evaluators observed the rats' Vertical and horizontal activities within 5 minutes, and cleaned up the excreta after each experiment.

(4) Determination of 5-HT and BDNF levels

The changes of serum Brain-derived neurotrophic factor (BDNF), serotonin (5-HT) and serum Brain-derived neurotrophic factor (BDNF) were detected after modeling, intervention and ELISA kit. The reagent kit is from Beijing Andy Huatai Technology Co., Ltd.

2.6 Statistical Methods

SPSS 22.0 statistical software was used to select one-way analysis of variance and t-test methods for statistical processing of the data. The statistical results are expressed as x ± s, and P<0.05 indicates a statistically significant difference.

3. Results

(1) Effect of Tongdu Acupuncture Combined with Wuchen Tang on Behavioral Indicators of PSD Rats

The results are shown in Table 1 and Table 2. Compared with the Sham surgery group, the Zea Longa Neuroethology score of rats in the model group increased significantly after modeling, while the percentage of sucrose water consumption, the horizontal movement score of open box experiment and the vertical movement score of open box experiment decreased significantly, and these behavioral indicators did not improve significantly after intervention. Compared with the model group, these behavioral indicators were significantly improved after treatment with Tongdu acupuncture, Tongdu acupuncture combined with Wuchen decoction, and the improvement effect of Tongdu acupuncture combined with Wuchen decoction was better than that of Tongdu acupuncture.

Table 1: Zea Longa Neuroethology score and sucrose water consumption percentage of rats in each group

Group	Zea Longa Neuroethology Score		Sucrose water consumption percentage (%)	
	After molding	After intervention	After molding	After intervention
Sham surgery group	0.00 ± 0.00	0.00 ± 0.00	77.21 ± 8.91	72.79 ± 6.09
Model Group	2.82 ± 0.36	2.69 ± 0.39[#]	55.27 ± 4.91	52.11 ± 3.92[#]
Tongdu Acupuncture Group	2.74 ± 0.41	1.76 ± 0.23[*]	56.17 ± 7.01	65.32 ± 5.15[*]
Tongdu Acupuncture Combined with Wuchen Tang Group	2.84 ± 0.39	1.24 ± 0.19[*&]	53.19 ± 5.27	69.07 ± 6.32[*&]

Note: Compared with the Sham surgery group, # P < 0.05; Compared with the model group, * P<0.05; Compared with the Tongdu acupuncture group,&P<0.05.

Table 2: Horizontal and Vertical Motor Scores in Open Box Experiments of Rats in Each Group

Group	Open box experiment horizontal motion score		Vertical motion scoring in open box experiments	
	After molding	After intervention	After molding	After intervention
Sham surgery group	70.08 ±6.32	73.79 ± 7.96	17.21 ± 0.91	15.92 ± 1.09
Model Group	42.82 ± 4.39	46.97 ± 4.59[#]	8.27 ± 0.91	10.11 ± 1.32[#]
Tongdu Acupuncture Group	44.06 ±5.01	56.28 ± 4.23[*]	9.71 ± 1.19	12.21 ± 1.15[*]
Tongdu Acupuncture Combined with Wuchen Tang Group	42.84 ± 4.05	64.09 ±5.91[*&]	9.19 ± 1.27	14.07 ± 1.32[*&]

Note: Compared with the Sham surgery group, # P < 0.05; Compared with the model group, * P<0.05; Compared with the Tongdu acupuncture group,&P<0.05.

(2) Effect of Tongdu Acupuncture Combined with Wuchen Tang on 5-HT and BDNF in Serum of PSD Rats

The results are shown in Table 3. Compared with the Sham surgery group, the levels of 5-HT and BDNF in the serum of the model group rats were significantly reduced. Compared with the model group, the levels of 5-HT and BDNF in the serum of rats were significantly increased after treatment with Tongdu acupuncture, Tongdu acupuncture combined with Wuchen decoction, and the improvement effect of Tongdu acupuncture combined with Wuchen decoction was better than that of Tongdu acupuncture.

Table 3: Effects of 5-HT and BDNF contents in serum of rats in each group

Group	5-HT (μg/L)	BDNF (ng/mL)
Sham surgery group	30.09 ± 2.97	52.17 ± 4.09
Model Group	14.27 ± 1.39[#]	32.91 ± 2.29[#]
Tongdu Acupuncture Group	21.36 ± 2.31[*]	41.23 ± 3.15[*]
Tongdu Acupuncture Combined with Wuchen Tang Group	26.14 ± 2.19[*&]	49.07 ± 3.92[*&]

Note: Compared with the sham surgery group, # P<0.05; Compared with the model group, * P<0.05; Compared with the Tongdu acupuncture group,&P<0.05.

4. Discussion

Post stroke depression is a complication of stroke, commonly referred to as "depression syndrome" [9]. Traditional Chinese medicine has a clear differentiation and treatment of stroke and depression syndrome, but there is no unified standard for post stroke depression [10]. At present, the main methods for treating PSD in traditional Chinese medicine are traditional Chinese medicine treatment, acupuncture treatment, and some other treatment methods. Some empirical formulas have been used to treat PSD, such as. The drugs in Chaihu Jialonggu Oyster soup can regulate qi and blood, relieve depression and phlegm, soothe liver and promote gallbladder, so it can improve the depressive symptoms of PSD patients [11-13]. Buyang Huanwu Tang not only improves the mental state of patients with post-stroke depression, but also improves their physical condition. In addition to oral administration of traditional Chinese medicine, some external uses of traditional Chinese medicine are also used to treat PSD. Some studies have selected the method of burying pills at the seed ear point of Wang Buliuxing to treat depression and anxiety symptoms in PSD patients. Acupuncture is also widely used in the treatment of PSD [14]. In clinical practice, acupuncture at the original point of the liver meridian, Taichong point, can dredge liver qi and regulate emotions [15]. In addition, the connection between the Du meridian and the liver meridian of Foot Jueyin intersects at the summit, proving that the relationship between the liver meridian and the brain is equally inseparable [16-17]. PSD corresponds to the relevant syndrome types of "stroke and depression syndrome" in traditional Chinese medicine, so the pathogenesis is mostly emotional discomfort and qi stagnation [18]. Therefore, the treatment is often combined with acupoints such as opening the orifices and awakening the mind, soothing the liver and regulating qi on the basis of promoting blood circulation and resolving stasis, which will have a more prominent therapeutic effect [19]. The research results indicate that the Tongdu Yishen acupuncture method can effectively treat PSD, and it can not only improve the adverse psychological state of PSD patients, but also promote the recovery of neurological function [20].

There are many risk factors for the onset of PSD, and the pathogenesis is complex, which also brings great difficulties to the treatment of PSD [21-23]. At present, the treatment of PSD is mainly through Western medicine, and it can indeed effectively treat PSD [24]. However, there are still some shortcomings, such as the defect of delayed onset and long-term toxic side effects of medication. Compared to Western medicine, traditional Chinese medicine has not yet been widely used in the treatment of PSD, but many research results have shown that traditional Chinese medicine can effectively treat PSD [25]. Therefore, searching for traditional Chinese medicine treatment methods to treat PSD is an effective approach [26-27]. Both traditional Chinese medicine and acupuncture can provide comprehensive treatment for patients from multiple perspectives [28-29]. The combination of acupuncture and traditional Chinese medicine therapy can exert dual advantages, balance multiple aspects, and improve overall efficacy [30].

5. Conclusion

Tongdu Acupuncture combined with Wushen Decoction can effectively treat PSD rats, which is mainly manifested in: significantly reducing the Zea Longa Neuroethology score of PSD rats, significantly increasing the percentage of sucrose water consumption, the score of open box horizontal exercise and open box vertical exercise, and significantly increasing the content of 5-HT and Brain-derived neurotrophic factor (BDNF) in the blood serum of PSD rats.

Acknowledgements

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