

Clinical Study of Acupuncture Combined with Transcranial Direct Current Stimulation on Vascular Dementia

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Keywords

vascular dementia, acupuncture, transcranial direct current, cognitive function, life ability

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Abstract

Background The study is to explore the clinical efficacy of acupuncture combined with transcranial direct current stimulation (tDCS) in the treatment of vascular dementia (VD). **Methods** A total of 100 VD patients were selected and randomly divided into a control group and an observation group, with 50 cases in each group. Patients in control group were given tDCS, while those in observation group were given tDCS combined with acupuncture. The clinical efficacy, mini mental state examination (MMSE) score, montreal cognitive function (MoCA) score, ability of daily living (ADL) score, blood rheology indexes, serum factor levels and adverse reactions were compared between the two groups. **Results** After treatment, the total effective rate of observation group (90.00%) was obviously higher than that of control group (70.00%) ($P<0.05$). Additionally, scores of MMSE and MoCA, as well as levels of serum brain-derived nerve growth factor (BDNF) and vascular endothelial growth factor (VEGF) after treatment were obviously higher than those before treatment ($P<0.05$), but score of ADL, level of matrix metalloproteinase-9 (MMP-9), whole blood high-/low-sheared viscosity and plasma viscosity after treatment were obviously lower than those before treatment ($P<0.05$), where changes in observation group were far more obvious than those in control group ($P<0.05$), with no serious adverse reactions in both groups during the treatment. **Conclusion:** With a certain degree of safety, acupuncture combined with tDCS shows great clinical efficacy in the treatment of VD patients through ameliorating the cerebral circulation and neuron function, as well as improving their cognitive function and living ability.



1. Introduction

Vascular dementia (VD) refers to hemorrhagic and ischemic cerebrovascular diseases-caused brain damage, which mostly occurs in the elderly (1, 2). Patients with VD are clinically characterized by functional declines in memory, cognition and behavior, which seriously affect their daily living ability and life quality. Currently, the clinical treatment of VD mainly resorts to conventional western medicine treatments such as control of blood pressure, blood sugar and blood lipid. Although certain effects have been obtained through the above-mentioned treatments, the overall effect is not satisfactory (3). In TCM, VD belongs to the category of "dilly" and "forgetfulness". Patients with mild VD feature as indifference, little speech and slow reaction, while those with severe VD show negligence, reversal of speech, neither knowing hunger nor knowing how to return, and incontinence, conspicuously affecting the patients' physical and mental health. VD acts on the brain, which as the palace of mentality and shrewdness, is closely related to the transformation and infusion of Yin essence and Yang Qi. The pathogenesis of VD lies in aging and body failure, deficiency of kidney essence, and difficulty in reaching the myeloid sea, which lead to the loss of nutrition in the myeloid sea as well as the disorders of mental activities and body machine. Loss of spleen and kidney transportation, internal stagnation and uneasy dissolution of phlegm turbidity, and phlegm and blood stasis result in cerebral marrow degeneration, brain depletion, spiritual disturbance and mental loss, which are the symptoms of dementia (4-6). Therefore, the treatment of VD needs to be performed through focusing on refreshing the brain, inducing resuscitation and replenishing Qi and blood. Some studies have demonstrated that transcranial direct current stimulation (tDCS), a new and safe non-invasive treatment method that can adjust the excitability of cerebral cortical nerve cells has a clinical application value in the treatment of cognitive dysfunction-related diseases (7). As reported by Tao Guo et al., tDCS can improve cognitive impairment through regulating oxidative stress, inflammation, and autophagy in a rat model of VD (8), indicating its

possible therapeutic role on VD. In addition, traditional Chinese medicine (TCM) therapy has made some progress in the clinical treatment of VD, a large number of literature have confirmed that acupuncture has a definite therapeutic effect on VD and has no toxic side effects (9, 10). Acupuncture refers to the use of needles at a certain angle to stimulate specific parts of the human body under the guidance of TCM theory, in order to achieve the goal of treating diseases (11). The previous study has revealed that the mechanism of acupuncture in the treatment of VD is related to the increase of cerebral blood flow and brain cell activity as well as the regulation on neurotransmitter release (12). More importantly, it has been found that the combined treatment of acupuncture and tDCS enhances the spontaneous conversation and naming in subacute vascular aphasia (13), proving its great potential in the treatment of neurological diseases. However, there are few studies established regarding the effect of combination of tDCS and acupuncture in the treatment of VD. Thus this study aims to explore the clinical efficacy and adverse effects of tDCS combined with acupuncture in the treatment of patients with VD, in order to provide a new clue for the clinical diagnosis and treatment of VD.

2. Materials and Methods

2.1 General information

A total of 100 VD patients who were admitted in our hospital from August 2017 to August 2019 were divided into an observation group (n=50) and a control group (n=50), according to the random number table method. There was no statistically significant difference in general information between the two groups ($P>0.05$), which therefore are comparable, as shown in Table 1. This study was approved by the Ethics Committee of the Xiaoshan District Hospital of Traditional Chinese Medicine, Hangzhou (Approval No. 2021026), and all the patients had signed the written informed consents. Patients who meet the diagnostic criteria of VD in the "Guidelines for the Diagnosis and Treatment of Vascular Cognitive Disorders" were included in this

research (14). However, patients were excluded if they had any of the following conditions: those with severe organ dysfunction diseases, such as heart, liver, and kidney dysfunction; those with other dementia diseases such as dementia with Lewy bodies, and

Alzheimer's disease; those with cognitive dysfunction caused by trauma; those who recently used sedatives, antidepressants and other drugs; those with severe infections and multiple organ failure.

Table 1 Comparison on general information between the two groups

Groups	Number of cases	Gender(Cases)		Underlying disease (Cases)			Degree of education (Cases)				
		Male	Female	Age(Years old)	Ischemic stroke	Hemorrhagic stroke	Course of diseases (Months)	Primary school	Junior high school	Senior high school	College and above
Observation group	50	28	22	67.24±6.23	37	13	4.21±0.76	16	13	11	10
Control group	50	29	21	69.12±5.56	35	15	4.18±0.63	18	12	10	10
χ^2/t		0.041		-1.592	0.198		0.215		0.205		
<i>P</i>		0.840		0.115	0.656		0.830		0.977		

2.2 Therapeutic methods

2.2.1 Control group

Patients in control group were given tDCS using a tDCS stimulator (Neuroconn, Germany). The dorsolateral prefrontal lobes of the patients' brain were stimulated by the anode of the tDCS stimulator, and the cathode was placed at the contralateral superior orbital margin, with a stimulation intensity of 1.2 mA and stimulation duration of 20 min, 1 time/day, for 5 consecutive days followed by a 2-day interval. The total treatment lasted 8 weeks.

2.2.2 Observation group

Based on the treatment of the control group, patients in observation group additively received acupuncture therapy. Concretely, the patients were placed in a supine position, and then the selection of acupoints including Shenting, Baihui, Shuigou, Laogong, Neiguan, Daling, and Shenmen was performed. After the routine disinfection of these acupoints, acupuncture needles (0.35 mm×40 mm) were used to perform acupuncture. Specifically, horizontal insertion

of needle was conducted at the acupoints of Shenting and Baihui 0.3 inches deep into the skin at 30 degrees, followed by a puncture of the Shougou 0.2 inches deep into the skin at a diagonally upward direction, and a straight piercing at Laogong, Neiguan, Daling and Shenmen with a depth of 0.3 inches into the skin. After the gain of gas at each acupoints, the even reinforcing-reducing technique was applied with 30-min needle retention and 1-min needle manipulation conducted every 10 min. The acupuncture therapy was performed 1 time/day, for 5 consecutive days, followed by a 2-day interval. The total treatment period was 8 weeks.

2.3 Observational indexes

2.3.1 Clinical efficacy

The clinical efficacy after treatment was evaluated between the two groups according to the "Guiding Principles for Clinical Research of New Chinese Medicines" (15). The specific efficacy criteria was listed below: markedly effective: efficacy index ≥20%; effective: 12%≤ efficacy index <20%; invalid:

efficacy index <12%. Total effective rate= (Markedly effective + Effective) cases / Total number of cases × 100%. Efficacy Index= (Post-treatment mini-mental state examination (MMSE) score - Pre-treatment MMSE score) / Pre-treatment MMSE score.

2.3.2 Mental status, cognitive function and living ability

Before and after treatment, the mental status, cognitive function and living ability of the patients were evaluated by the MMSE score, which includes memory, attention, numeracy, orientation, and language skills, with a total score of 30 (16). A higher MMSE score indicates a better cognitive function. Montreal cognitive function (MoCA) score was used to evaluate the cognitive function of patients in the two groups, which mainly included 7 items such as language ability, orientation, attention and memory, with a total score 30. The higher the MoCA score, the better the cognitive function of patients (17). The daily living ability of patients in the two groups was evaluated by the ability of daily living (ADL) score, which comprises the physical ADL and instrumental ADL scales (18). The ADL score has a total of 14 items, and 4 grades, where grade 1 represents that the patients can complete the daily events on their own without difficulty, grade 2 signifies that the patients can finish the daily events on their own with some difficulties, grade 3 suggests that the patients can complete the daily events on their own under the help of others, and grade 4 means that the patients are unable to complete the basic daily events. The ADL score has a total score of 56, with a higher score indicating a worse ability of daily living of patient.

2.3.3 Hemorheology indexes

The fasting peripheral venous blood (3 ml) from the patient before and after treatment was collected, and the whole blood high-/low-sheared viscosity, and plasma viscosity were analyzed by a blood analyzer (BC-5140, Mindray, China).

2.3.4 Serum factor levels

After the collection of the fasting peripheral venous blood (3 ml) from the patient before and after treatment, the serum levels of brain-derived nerve growth factor (BDNF) (1533660614, Jianglai Biotechnology, China), vascular endothelial growth factor (VEGF) (KHG0111, life-Invitrogen, USA), and matrix metalloproteinase-9 (MMP-9) (EK0465, Sciencell, USA) were detected by corresponding enzyme-linked immunosorbent assay (ELISA) kits.

2.3.5 Adverse reactions

The incidence of adverse reactions in patients of both groups after treatment was observed and recorded.

2.4 Statistical analysis

Statistical analysis was performed using SPSS 22.0. Enumeration data were compared by the χ^2 test. Measurement data were presented as mean ± standard deviation ($\bar{x} \pm s$), and compared by the *t* test. *P*<0.05 was considered statistically significant.

3. Results

3.1 Acupuncture increased the total effective rate of patients treated with tDCS

The total effective rate of the observation group (90.00%) after treatment was prominently higher than that of the control group (70.00%) (*P*<0.05), as shown in Table 2.

Table 2 Comparison on clinical efficacy between the two groups (cases)

Groups	Number of cases	Markedly effective	Effective	Invalid	Total effective rate (%)
Observation group	50	30	15	5	45(90.00)
Control group	50	15	20	15	35(70.00)
χ^2					6.250
<i>P</i>					0.012

3.2 Acupuncture increased the MMSE and MoCA scores but decreased the ADL score of patients

treated with tDCS

Before treatment, there was no significant difference in the MMSE, MoCA and ADL scores between the two groups ($P>0.05$). The MMSE and MoCA scores of both groups after treatment were distinctly higher than those before treatment ($P<0.05$), whereas the ADL score of the two groups after treatment was significantly lower than that before treatment ($P<0.05$). Meanwhile, changes in observation group were more obvious than those in control group, as shown in Table 3.

3.3 Acupuncture lowered the hemorheology indexes of patients treated with tDCS

Before treatment, there was no significant difference in the whole blood high-/low-sheared viscosity, and plasma viscosity between the two groups ($P>0.05$). However, the whole blood high-/low-sheared viscosity, and plasma viscosity of the two groups after treatment were dramatically lower than those before treatment ($P<0.05$), and these indexes of the observation group were evidently lower than those of the control group ($P<0.05$), as depicted in Table 4.

Table 3 Comparison on the MMSE, MoCA and ADL scores between the two groups

Groups	Number of cases	MMSE		MoCA		ADL	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	50	16.67±2.65	21.67±2.23 ^a	14.54±2.65	18.65±2.09 ^a	41.23±7.87	28.98±5.76
Control group	50	16.23±2.87	20.24±2.15 ^a	14.78±2.87	16.98±2.56 ^a	40.89±7.65	37.87±5.98
<i>t</i>		0.796	3.264	-0.434	3.573	0.219	-7.628
<i>P</i>		0.428	0.002	0.665	0.001	0.827	<0.001

Note: Compared with those before treatment, ^a $P<0.05$

Table 4 Comparison on hemorheology indexes between the two groups ($\bar{x}\pm s$)

Groups	Number of cases	Whole blood high-sheared viscosity (mPa·s)		Whole blood low-sheared viscosity (mPa·s)		Plasma viscosity (mPa·s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	50	6.50±0.45	4.56±0.35 ^a	14.21±2.24	10.87±2.03 ^a	1.87±0.12	1.15±0.12 ^a
Control group	50	6.45±0.50	5.65±0.38 ^a	14.56±2.76	12.23±2.11 ^a	1.85±0.11	1.39±0.16 ^a
<i>t</i>		0.526	-14.919	-0.696	-3.284	0.869	-8.485
<i>P</i>		0.600	<0.001	0.488	0.001	0.387	<0.001

Note: Compared with those before treatment, ^a $P<0.05$

3.4 Acupuncture increased the BDNF and VEGF levels but decreased the MMP-9 level of patients treated with tDCS

Before treatment, there was no significant difference in the levels of BDNF, VEGF and MMP-9 between the two groups ($P>0.05$). The levels of BDNF and VEGF of the two groups after treatment and of the

observation group were sharply higher than those before treatment and those of the control group, respectively ($P<0.05$). However, the level of MMP-9 of the two groups after treatment and of the observation group was notably lower than that before treatment and that of the control group, respectively ($P<0.05$), as described in Table 5.

3.5 The combination of acupuncture and tDCS showed safety to VD patients

During the whole treatment, neither serious adverse

reactions nor phenomena such as infection, needle sickness and broken needles, was observed in both groups.

Table 5 Comparison on serum factor levels between the two groups

Groups	Number of cases	BDNF(ng/ml)		VEGF(ng/ml)		MMP-9(pg/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	50	20.45±6.78	35.65±8.78 ^a	78.76±6.75	86.98±7.32 ^a	34.12±3.12	25.09±2.12 ^a
Control group	50	20.91±6.45	29.87±7.86 ^a	78.92±6.87	82.75±7.65 ^a	34.56±3.54	27.65±2.45 ^a
<i>t</i>		-0.348	3.468	-0.117	2.825	-0.660	-5.587
<i>P</i>		0.729	0.001	0.907	0.006	0.511	<0.001

Note: Compared with those before treatment, ^a*P*<0.05

4. Discussion

In this study, the clinical total effective rate and the MMSE and MoCA scores of the observation group were strikingly higher than those of the control group, and the ADL score of the observation group was prominently lower than that of the control group, indicating that acupuncture combined with tDCS exerts a definite therapeutic effect on VD patients, and can effectively ameliorate the patient's mental status, cognitive function, and daily living ability. The tDCS is a new technology that can change the excitability of the brain via a constant current to the brain scalp, with no invasiveness and low intensity (19). In this study, the patient's dorsolateral prefrontal lobe was stimulated with the anode, and the cathode was placed on the contralateral superior orbital margin. After a weak direct current was applied to the cerebral cortex, the distribution of the neuron membrane potential charges was changed. Subsequently, the depolarization and hyperpolarization were generated, both of which can enhance the cortical excitability of the brain, and thus regulate brain function to improve the clinical symptoms of VD patients as well as their cognitive function and daily living ability (20, 21). In addition, in acupuncture therapy, Baihui, also known as Three Yang-Five Hui, is the acupoint where eight vessels congregate (22). Acupuncture at Baihui can

induce resuscitation and refresh the brain, dissolve phlegm and soothe the wind, and lift Yang Qi and solidify the viscera (22). Shenting is the acupoint of Zangyuan, acupuncture at Shenting can strengthen the brain and improve the intelligence (23). Shuigou is the confluence of the governor vessels and the meridian of Yang Ming of the hands and feet, acupuncture at Shuigou can link up the Qi from heaven and from the earth (24). Acupuncture at Baihui, combined with Shenting and Shuigou, can dredge the marrow sea and adjust Qi and blood. Neiguan is the collateral point in the pericardium meridian of hand Jueyin, acupuncture at Neiguan can regulate Qi and relieve pain, soothe the heart and calm the mind (25). Daling acupoint is one of Sun Zhenren's thirteen ghost acupoints, acupuncture at Daling can relieve fire and develop Qi (26). Matching with Daling during acupuncture at Neiguan can cure mental disturbances, and supplementation with acupuncture at Shenmen and Laogong acupoints can soothe the heart, calm the mind and replenish the heart-Qi (26). Acupuncture at all these acupoints can refresh the brain, induce resuscitation, and replenish Qi and blood (27). One previous research has signified that the blood rheology of VD patients changed abnormally, as manifested in increased blood viscosity and hindered blood perfusion, which can induce ischemia and

hypoxia in the bodies' brain tissue, resulting in damage to the body's neurons and affected function of the brain tissue (28), which was consistent with the results in this study. BDNF, belonging to the family of neurotrophic factors, can promote regeneration of neurons, repair and protect neurons, thereby maintaining the normal function of the body's nervous system. VEGF is an angiogenic growth factor that can promote blood vessel growth, increase blood supply to brain tissues, and protect the nervous system (29). MMP-9 is a gelatinase that can degrade extracellular matrix and damage body neurons (30). In this study, after treatment, whole blood high-sheared viscosity, whole blood low-sheared viscosity, plasma viscosity, and MMP-9 levels of observation group were clearly lower than those of the control group, but the levels of BDNF and VEGF were evidently higher than those of the control group, suggesting that acupuncture combined with tDCS can promote blood circulation in the brain and improve nerve function in VD patients. Another study has illustrated that through weak electrical energy, tDCS stimulates the central nervous system of the brain, increases cerebral blood flow perfusion in the corresponding parts of the dorsolateral prefrontal cortex, facilitates the cerebral blood flow, improves brain microcirculation, regulates blood-oxygen saturation, and promotes expansion of cerebral vessels, thus initiating the endogenous neuroprotective mechanism of the brain to repair the body's brain damage (31), which were similar to our findings that tDCS could protect against neuron injury. At the same time, in the acupuncture therapy, acupuncture at Baihui can enhance the excitability of the relevant parts under the cerebral cortex, alleviate local vascular spasm, accelerate blood circulation in the brain, and improve the metabolic function of neurons in the body. Acupuncture at specific acupoints such as Neiguan and Shuigou can stimulate the body's ischemic and hypoxic brain tissue to establish collateral circulation, expand cerebral blood vessels, increase cerebral blood flow, inhibit neuronal apoptosis, and ameliorate neuronal function (32), and these findings were in line with our results that acupuncture could alleviate the damage to nervous

system of VD patients. In addition, during the whole treatment, no serious adverse reactions were observed in patients of the two groups, and no infection and needle sickness occurred during the process of acupuncture, which suggest that acupuncture combined with tDCS has a certain degree of safety.

5. Conclusion

Acupuncture combined with tDCS shows great clinical efficacy in the treatment of patients with VD through ameliorating the patients' blood circulation in the brain and their neuron functions, as well as improving their cognitive function and living ability, with a certain degree of safety.

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Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization, R.J.C; Data curation, H.L; Formal analysis, R.J.C; Methodology, H.L; Writing-Original draft, R.J.C; Writing-review and editing, R.J.C; All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Xiaoshan District Hospital of Traditional Chinese Medicine, Hangzhou (Approval No. 2021026), and all the patients had signed the written informed consents.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable

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