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The effect of scalp electroacupuncture combined with Memantine in patients with vascular dementia

A retrospective study

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Abstract

Currently there is no effective treatment for vascular dementia (VaD). Pharmacological treatment often lead to severe complications and require drug dosage adjustment. This study investigated the effect of scalp electroacupuncture combined with Memantine in VaD. The safety and antioxidative effect of scalp electroacupuncture were also explored.

A retrospective study was conducted and data of inpatients of Linyi Central Hospital with VaD between June 2017 and May 2018 were collected and sorted. The patients were divided into scalp electroacupuncture-medication (A), scalp electroacupuncture (B) and medication (control) (C) groups, in which Memantine was prescribed as medication. Cognitive function, activities of daily living and quality of life assessed by Montreal Cognitive Assessment (MoCA), Barthel index and dementia quality of life questionnaire; the contents of superoxide dismutase, lipid peroxide and nitric oxide in blood samples; and adverse reaction were compared.

Data from a total of 150 patients were collected (Group A, n = 55; Group B, n = 50; Group C, n = 45). The post-treatment/follow-up Montreal Cognitive Assessment, Barthel index and dementia quality of life questionnaire scores were significantly improved in all groups compared to pre-treatment (groups A and B, $P<.01$; group C, $P<.05$). The improvements were significant for groups A vs C, B vs C ($P<0.01$, both), and group A vs B ($P<.05$). The post-treatment/follow-up levels of lipid peroxide and nitric oxide decreased significantly while superoxide dismutase increased significantly in groups A and B compared to pre-treatment ($P<.01$, both). The differences were significant for groups A vs C, and B vs C ($P<.01$, both), but not significant between groups A and B ($P>.05$). There were no significant adverse events occurred during the study and follow-up.

In combined treatment, scalp electroacupuncture works in parallel with Memantine and significantly increase the therapeutic effect in VaD with no significant adverse events. Scalp electroacupuncture may have the potential to serve as an option or alternative treatment for VaD. Scalp electroacupuncture may alleviate VaD symptoms through its antioxidative mechanism.

Abbreviations: AD = Alzheimer's disease, ANOVA = analysis of variance, BI = Barthel index, CDR = clinical dementia rating, DEMQOL = dementia quality of life questionnaire, LPO = lipid peroxide, MoCA = Montreal Cognitive Assessment, NO = nitric oxide, ROS = reactive oxygen species, SOD = superoxide dismutase, VaD = vascular dementia.

Keywords: memantine, scalp electroacupuncture, vascular dementia

Editor: Yi Zhu.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement: All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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How to cite this article: Yue A, Han X, Mao E, Wu G, Gao J, Huang L, Zhou B. The effect of scalp electroacupuncture combined with Memantine in patients with vascular dementia: a retrospective study. Medicine 2020;99:33(e21242).

Received: 26 February 2020 / Received in final form: 12 May 2020 / Accepted: 11 June 2020

http://dx.doi.org/10.1097/MD.0000000000021242

1. Introduction

Vascular dementia (VaD) is the second most common type of dementia after Alzheimer's disease (AD),[1] accounting for 15% to 20% of all cases.[2] Unlike AD, there are currently no licensed treatments for VaD,[1] and its mean survival rate is lower than AD.[3] VaD is characterized by cognitive impairment and cerebrovascular pathologies[4] caused by brain damage due to impaired blood flow over a long period of time.[5] VaD and cerebrovascular diseases have the common risk factors, including hypertension, diabetes, obesity, and hyperlipidemia.[6–9] Other risk factors for VaD are aging, atherosclerosis and stroke.[10]

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species (ROS) and the biological system ability to readily detoxify the reactive intermediates.[11] It has been demonstrated to involve in the pathogenesis of AD and VaD. Researches have been conducted to investigate if antioxidant therapy exerts a role in the prevention and treatment of these diseases.[12] Previous researches have also highlighted the importance of oxidative stress in both normal and pathological brain aging.[13] Oxidative stress is not only linked to VaD, but also to all its risk factors.[12]

The current treatment for VaD such as antioxidants, antiinflammatory agents or agents increasing cerebral perfusion have not yield satisfactory results.[5] Pharmacological treatment often lead to severe complications due to hypersensitivity of the brain in patients with dementia and decrease of hepatic and kidney drug metabolism with advance age. The drug dosage often requires regular adjustment.[14–16] Early evidence suggests that multifactorial interventions may prevent or delay the onset of dementia.[17]

Acupuncture is often used as a treatment for dementia.[18,19] It can relieve VaD symptoms with minimal side effects, improve cognitive and emotional capabilities,[20] and reduce VaD severity.[21] Electroacupuncture reduces functional deficits of neuropathy,[22] prevents cognitive deficiency,[23] and significantly improves learning and memory capacity.[24] Scalp acupuncture stimulates the lesion area on the scalp to produce therapeutic effects.[25] Its efficacy for VaD has been confirmed by numerous empirical clinical studies.[26–28] It can also improve the clinical intelligence level of VaD patients.[29]

Studies have shown that the cognitive enhancing effect of acupuncture is likely to be at least partially attributable to decreased oxidative stress.[30] Liu et al[31,32] found that acupuncture could improve memory impairment through increasing antioxidant system ability in hippocampus of VaD rats. Experimental studies reported that electroacupuncture could effectively attenuate lipid peroxidation content through increasing antioxidant enzyme activities such as superoxide dismutase (SOD) in hippocampal CA1 of VaD rats.[33,34] Previous study found that inducible nitric oxide (NO) synthase expression and NO production in glial cells can cause NO diffusion and neurotoxicity which exacerbate delayed infarct expansion and play a key pathological role in ischemic injury.[35] Increasing evidences suggested that the neurotoxic effects of inducible NO synthase derived NO could aggravate cerebral ischemia/reperfusion injury,[36] while electroacupuncture could provide neuroprotection against delayed infarct expansion and subsequently reduce oxidative stress in cerebral ischemia/reperfusion injury.[37] These observations suggested that acupuncture may alleviate VaD symptoms through its antioxidative mechanism.

Memantine is a moderate-affinity, uncompetitive NMDA receptor antagonist that has been shown to have therapeutic potential in numerous central nervous system disorders without undesirable side effects.[38] It has been shown to prevent neurodegeneration and learning deficits in animal models of dementia,[39,40] and reduce neuronal damage in global and focal animals models of brain ischemia.[41,42] Previous study revealed significant neuroprotective activity against oxidative stress from antioxidant properties of Memantine derivatives.[43]

In this study, we compared the effect of scalp electroacupuncture combined with Memantine, scalp electroacupuncture and Memantine in patients with VaD. Safety evaluation was performed, and the antioxidative effect of scalp electroacupuncture in VaD treatment was explored. We hypothesized that combination with scalp acupuncture would increase the therapeutic effect of Memantine in VaD treatment. The findings of the present study may help to provide more clinical evidence to develop a novel therapeutic approach for VaD.

2. Materials and methods

2.1. Patients

A retrospective review was performed and data for all inpatients of Linyi Central Hospital diagnosed with VaD between June 2017 and May 2018 were collected and sorted. The patients who met the criteria for probable VaD as defined by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences[44] or diagnostic criteria for dementia in the Diagnostic and Statistical Manual of Mental Disorders (4th Edition).[45] Inclusion criteria: symptoms of dementia; acute onset or a step-progressive duration of the illness; definite signs of dementia; mild (clinical dementia rating [CDR] = 1.0) or moderate (CDR = 2.0) CDR[46]; Hachinski ischemia score ≥ 7[47]; a noticeable cerebrovascular pathologic changes detected by CT or MRI; availability of a reliable caregiver. Exclusion criteria: prior diagnosis of AD, Parkinson disease, Huntington disease, or other neurodegenerative dementia; presence of abnormal executive control function; inability to give consent; severe neurological deficits; severe mental disorders. The details collected included baseline data (age, gender, duration of VaD, education, location of lesion, diagnosis, and comorbidities), therapeutic outcome (cognitive function, activities of daily living and quality of life assessed by Montreal Cognitive Assessment (MoCA), Barthel index (BI) and dementia quality of life questionnaire (DEMQOL), levels of SOD, lipid peroxide (LPO) and NO, and adverse events occurred. The data were sorted by 2 researchers independently and crosschecked. Any discrepancies would be discussed with a third researcher. This retrospective study was approved by the Ethics Committee of Linyi Central Hospital (No. LCN201704169) and the requirement for informed consent was waived.

2.2. Grouping

The participants were divided into: scalp electroacupuncture-medication group (A), scalp electroacupuncture group (B) and medication group (control) (C). Memantine 10 mg twice daily was prescribed for medication.

2.3. Treatment and follow-up

The patients received a total course of 6-week treatment and a 4-week post-treatment follow-up. Evaluation were performed

after completed treatment and at the end of follow-up. They were allowed to continue medications for lowering blood pressure and cholesterol. The patients were contacted regularly by the staffs to remind them for subsequent visits, which helped to minimize drop-out rates.

2.4. Treatment procedure

The subjects in groups A and B received scalp electroacupuncture. Based on the results of previous studies[48] the acupoints Sishencong (EX-HN 1), Baihui (GV 20), Shenting (GV 24) and (bilateral) Fengchi (GB 20) were applied for treatment. Disposable Chinese acupuncture stainless filiform needles (Hwato brand, Suzhou Medical Appliances Factory, Suzhou, Jiangsu, P.R. China) size 0.30 mm x 40 mm were used. All needles were sterilized with 75% alcohol before use. With the patient in sitting position, the area around the acupoints were disinfected with 75% alcohol. For Fengchi acupoint, the needles were punctured obliquely into a depth of 15 to 30 mm. For remaining acupoints, by forming an angle of 15°-30° with the scalp, the needles were penetrated obliquely into a depth of 15 to 25 mm. After deqi, the needles were connected to an electrical stimulator (G6805-2, Shanghai Huayi Medical Instrument Co., Ltd, Shanghai, P.R. China), continuous wave, frequency 3 to 15 Hz, and current intensity 2 to 4 mA (stimulation depended on patients tolerance). Shenting (GV 24), Baihui (GV 20), left and right Sishencong (EX-HN 1) formed a group of acupoints; anterior and posterior Sishencong (EX-HN 1), and left and right Fengchi (GB 20) formed a group of acupoints. Both groups were applied alternately. Shenting (GV 24) was connected to the positive electrode, left Sishencong (EX-HN 1) was connected to the negative electrode; Baihui (GV 20) was connected to the positive electrode, right Sishencong (EX-HN 1) was connected to the negative electrode; anterior Sishencong (EX-HN 1) was connected to the positive electrode, left Fengchi (GB 20) was connected to the negative electrode; posterior Sishencong (EX-HN 1) was connected to the positive electrode, right Fengchi (GB 20) was connected to the negative electrode. Each treatment lasted for 30 minute, once a day, 5 days per week, for 6 weeks.

All patients were treated by a licensed traditional Chinese medicine practitioner with over 15 years of experience. Participants in Groups A and C received Memantine (Bayer Healthcare Co., Ltd., Beijing, China) 10 mg twice daily, for 6 weeks.

2.5. Observation of therapeutic efficacy

The MoCA, BI, and DEMQOL were measured within 24 hour of admission, after completed treatment and at the end of follow-up. The levels of SOD, LPO, and NO were also evaluated. 10 mL of venous blood was drawn from all patients after overnight fasting. Reagents and detection kits were purchased from Nanjing Jiancheng Bioengineering Institute Co., Ltd., Nanjing, Jiangsu, P. R. China. The evaluation was performed by assessors who were blinded with the type of treatment the patients received.

2.6. Safety evaluation

Any adverse events were recorded and intervention would be stopped immediately. Acupuncture-related adverse events included cases of needle site bleeding, hematoma, increase pain, fainting, and local infection. Vital signs (temperature, heart rate, blood pressure), and physical examination were performed during each visit.

2.7. Main outcome measures

The primary outcome measure was the therapeutic effect. The secondary outcome measure was safety evaluation, and the antioxidative effect.

2.8. Statistical analysis

Data were presented as mean ± standard deviation for continuous variables or percentages for categorical variables. For baseline characteristics, enumeration data of each variable were compared with Chi-square test, while the measurement data were compared with analysis of variance (ANOVA) test. For evaluation of the therapeutic effect and antioxidative effect, nonparametric ANOVA (Kruskal-Wallis H test) followed by pairwise multiple comparisons were used to compare the pre-/post-treatment or pre-treatment/follow-up differences of the same group. Wilcoxon signed-rank test was used for comparisons with the control group. Statistical analysis was performed using SPSS software (version 19.0, SPSS, Chicago, Illinois) and R version 2.4.1. $P < .05$ was considered as statistically significant. The analyzes were performed on intention-to-treat basis, with missing data replaced by last observation carried forward. Intention-to-treat analysis evaluates treatment effects over the population with at least 1 post-treatment evaluation. The last observation carried forward ANOVA performs statistical test for treatment effects by treating the last observation prior to drop-out as the observation from the last visit.

3. Results

Data from a total of 150 subjects were collected. Group A, n = 55; Group B, n = 50; Group C, n = 45). There were 3 missing data, 1 from each group due to loss to follow-up.

3.1. Baseline characteristics

The 3 groups were comparable with regard to baseline characteristics ($P > .05$) (Table 1). Figure 1 showed typical CT and MRI images of a patient with multi-infarct dementia.

3.2. Assessment

The post-treatment/follow-up MoCA, BI and DEMQOL scores were significantly improved in all groups compared to pre-treatment (groups A and B, $P < .01$; group C, $P < .05$). The improvements were significantly different (group A vs C and group B vs C, $P < .01$; group A vs B, $P < .05$) (Table 2 and Supplementary Table 1, http://links.lww.com/MD/E619).

3.3. Adverse events reporting

There were no acupuncture-related adverse events occurred during the study and follow-up.

3.4. Test indicators

The post-treatment/follow-up levels of LPO and NO decreased significantly while SOD increased significantly in groups A and B compared to pre-treatment ($P < .01$, both). The differences were significant for groups A vs C and B vs C ($P < .01$, both), but not significant between group A and B ($P > .05$) (Table 3).

Table 1

Baseline characteristics.

Variable	Scalp electroacupuncture-medication (Group A, n=55)	Scalp electroacupuncture (Group B, n=50)	Medication (control) (Group C, n=45)	*P* value
Gender, n (%)				
Male	41 (74.5)	38 (76.0)	34 (75.6)	
Female	14 (25.5)	12 (24.0)	11 (24.4)	.12
Age (yr)	66.1±7.0	66.7±7.5	66.5±7.2	.51
Duration of VaD				
≤3 mo	25 (45.4)	22 (44.0)	20 (44.4)	
3 mo - ≤ 1 yr	12 (21.8)	11 (22.0)	10 (22.2)	
1-2 yr	9 (16.4)	9 (18.0)	8 (17.8)	
≥2 yr	9 (16.4)	8 (16.0)	7 (15.6)	.26
Education (yr)				
0	6 (11.0)	6 (12.0)	5 (11.1)	
1-6	8 (14.5)	8 (16.0)	7 (15.6)	.33
7–9	30 (54.5)	27 (54.0)	24 (53.3)	
≥10	11 (20.0)	9 (18.0)	9 (20.0)	
Location of lesion				
Left-sided lesions	19 (34.6)	17 (34.0)	15 (33.3)	
Right-sided lesions	23 (41.8)	21 (42.0)	19 (42.2)	
Bilateral lesions	13 (23.6)	12 (24.0)	11 (24.5)	.19
Diagnosis				
Infarct dementia	46 (83.6)	42 (84.0)	37 (82.2)	
Multi infarct	10	10	8	
Strategic infarct	8	7	7	
Small vessel	28	25	22	
Hemorrhagic dementia	4 (7.3)	3 (6.0)	3 (6.7)	
Mixed dementia	5 (9.1)	5 (10.0)	5 (11.1)	.28
Comorbidities				
Cardiological Cardiovascular disease	11 (20.0)	9 (18.0)	8 (17.8)	
Hypertension	27 (49.1)	26 (52.0)	23 (51.1)	
Vascular				
Atherosclerosis	7 (12.7)	7 (14.0)	8 (17.8)	
Stroke	7 (12.7)	6 (12.0)	6 (13.3)	
Metabolic/Endocrine				
Obesity	6 (10.9)	8 (16.0)	5 (11.1)	
Diabetes	7 (12.7)	5 (10.0)	6 (13.3)	.43

Note: Data were presented as mean±standard deviation or number of patients (n) with percentage (%). The *P* value indicated comparison among the 3 groups for each variable. The enumeration data were compared with Chi-square test, while the measurement data were compared with ANOVA test. Abbreviatons: MoCA = Montreal Cognitive Assessment, BI = Barthel index, DEMQOL = dementia quality of life questionnaire.

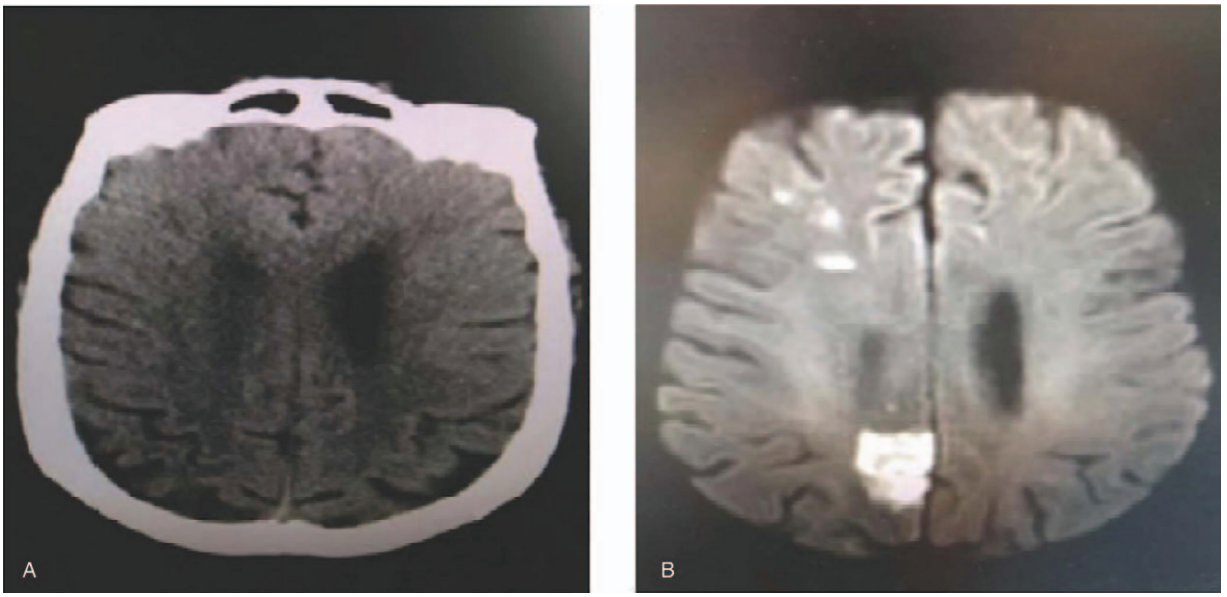

Figure 1. Typical (A) CT (B) MRI images of a patient with multi-infarct dementia. CT = computed tomography, MRI = magnetice resonance imaging.

Table 2

Therapeutic outcome.

Assessment scores	Scalp electroacupuncture- medication (Group A, n = 55)	Scalp electroacupuncture (Group B, n = 50)	Medication (control) (Group C, n = 45)
MoCA			
Pre-treatment	10.52 ± 1.51	10.48 ± 1.48	10.55 ± 1.53
Post-treatment	18.25 ± 3.26**††‡	16.21 ± 3.12**††	13.13 ± 3.01*
Follow-up	20.19 ± 3.30**††‡	17.66 ± 3.18**††	13.86 ± 3.05*
BI			
Pre-treatment	54.33 ± 7.15	54.26 ± 7.06	54.35 ± 7.19
Post-treatment	66.94 ± 9.45**††‡	64.59 ± 9.21**††	59.78 ± 8.69*
Follow-up	68.31 ± 7.39**††‡	65.82 ± 7.42**††	60.56 ± 7.56*
DEMQOL			
Pre-treatment	72.26 ± 6.05	71.39 ± 6.09	72.41 ± 6.18
Post-treatment	78.87 ± 6.71**††‡	76.69 ± 6.59**††	76.09 ± 6.52*
Follow-up	80.31 ± 7.01**††‡	77.89 ± 6.82**††	76.98 ± 6.72*

Note: Data were presented as mean±standard deviation or number of patients (n) with percentage (%).

MoCA = Montreal Cognitive Assessment, BI = Barthel index, DEMQOL = dementia quality of life questionnaire.

Pre- and post-treatment/follow-up differences between the same group, *$P<.05$, **$P<.01$; pre- and post-treatment/follow-up differences compared with group C, ††$P<.01$; pre- and post-treatment/follow-up differences between groups A and B, ‡$P<.05$.

As according to the results, the improvements were significantly different for group A vs C and group B vs C ($P<.01$, both) and group A vs B ($P<.05$).

The differences between groups A and C, and between groups B and C were $P<.01$ for both, which were presented as †† in the table.

4. Discussion

Studies have shown higher incidence of VaD in men than in women.[2] Females are at greater risk of developing AD, while males are at greater risk of developing VaD.[49] Between 1% and 4% of people over 65 years suffer from VaD,[50] while the prevalence appears to double every 5 to 10 years.[51] Advanced age and gender are 2 of the most prominent risk factors for dementia.[49] Previous systematic review[52] found association between lower education with greater risk for dementia in many but not all studies. The level of education associated with risk for dementia varied by study population, and more years of education did not uniformly attenuate the risk for dementia. The definition of low education may ranged from illiterate to less than 15 years, while the highest education level may ranged from literate to 17+ years. Some studies divided education into categories and identified each level as significant or not significant. In this study, the mean education duration (year) for group A, group B and group C was 7.01 ± 1.05, 7.12 ± 1.13, and 7.06 ± 1.08 respectively. If divided according to the number of years of education, the number of patients in the low education group (<10 years of education) was significantly higher than the high education (>10 years of education) ($P<.05$), and dividing into categories showed most patients received 7 to 9 years of education ($P<.05$, compared with other categories). It was suggested that the effect of education on risk for dementia may be best evaluated within the context of a lifespan developmental model.

Previous meta-analysis review indicated that acupuncture has neuroprotective, antioxidant and anti-apoptosis effect in VaD.[53] With the advance of new knowledge and technology, additional methods such as electroacupuncture and new acupuncture points are being developed.[54] Electropuncture substitutes for prolonged hand maneuvering and helps assuring that the patient gets the amount of stimulation needed. It also reduces the total treatment time by providing continued stimulus. The frequency and amount of stimulus are easier to control than with manual acupuncture, and its immediate effect was superior to acupuncture in VaD patients. A meta-analysis study on VaD treatment with different acupuncture methods found good therapeutic effect with electroacupuncture.[55]

Table 3

Test indicators.

Group	Total cases (n)		SOD (μmol/L)	LPO (μmol/L)	NO (μmol/L)
Scalp electroacupuncture- medication (Group A)	55	Pre-treatment	50.21 ± 1.21	5.64 ± 0.65	1.72 ± 0.21
		Post-treatment	58.17 ± 1.35**††	4.79 ± 0.35**††	1.32 ± 0.09**††
		Follow-up	58.89 ± 1.38**††	4.69 ± 0.31**††	1.24 ± 0.11**††
Scalp electroacupuncture (Group B)	50	Pre-treatment	50.23 ± 1.23	5.60 ± 0.54	1.72 ± 0.22
		Post-treatment	58.18 ± 1.36**††	4.76 ± 0.34**††	1.34 ± 0.12**††
		Follow-up	58.87 ± 1.37**††	4.68 ± 0.30**††	1.27 ± 0.13**††
Medication (control) (Group C)	45	Pre-treatment	50.25 ± 1.24	5.52 ± 0.42	1.66 ± 0.20
		Post-treatment	50.31 ± 1.25	5.31 ± 0.37	1.51 ± 0.15
		Follow-up	50.33 ± 1.25	5.27 ± 0.36	1.48 ± 0.14

Note: Data were presented as mean±standard deviation, n: number of patients.

SOD = superoxide dismutase, LPO = lipid peroxide; NO = nitric oxide.

Pre- and post-treatment/follow-up differences between the same group, *$P<.05$, **$P<.01$; pre- and post-treatment/follow-up differences compared with group C, ††$P<.01$.

As according to the results, the differences for test indicators were significant for groups A vs C and B vs C ($P<.01$, both), and not significant between group A and B ($P>.05$).

The differences between groups A and C, and between groups B and C were $P<.01$ for both, and were presented as †† in the table.

Scalp acupuncture is a modern innovation. Its intervention areas are based on the reflex somatotopic system organized on the scalp surface. The needles are subcutaneously inserted into various zones which are specific areas through which the central nervous system, endocrine system, and channels are transported to and fro. From a Western perspective, these zones are corresponded to the cerebrum and cerebellum areas responsible for motor activity, sensory, vision, speech, hearing, and equilibrium. Scalp acupuncture also helps to strenghten the immune system and prevent illness. It is less expensive, entails less risk, yield quicker responses, and causes fewer side effects than many pharmacological treatments. Its use as a main tool for rehabilitation is a relatively new concept.[54]

The results from this study shows that in group A, scalp electroacupuncture works in parallel with Memantine, and significantly improve the cognitive function, activities of daily living and quality of life in patients with VaD. The effect of scalp electroacupuncture alone (group B) is significantly stronger than Memantine (group C), suggesting the possibility of complete substitution of the medication with scalp electroacupuncture. Scalp electroacupuncture may have the potential to serve as an option or alternative treatment for VaD. Previous study reported low incidence of dizziness and constipation with Memantine in mild to moderate VaD. Despite this, overall it is well tolerated and safe.[56] Thus, combination with scalp electroacupuncture may reduce the dosage of the medication required to achieve similar therapeutic effect, and this may further reduce the risk of adverse events.

Baihui (GV 20), Sishencong (EX-HN 1), Shenting (GV 24) and Fengchi (SP 40) are among the frequently used acupoints in VaD treatment.[57] Baihui can decrease cerebral ischemic-reperfusion injury, and improve neurofunction.[58,59] Sishencong improves the quality of sleep.[60] Treatment at Baihui and Shenting can improve cognitive function.[61] Modern research shows that Baihui, Sishenchong and Shenting are located in the projection area of frontal, temporal and parietal lobes, which is closely related to human's advanced thinking, memory and mind.[62] Treatment at Fengchi (GB 20) can directly improve brain function.[63]

SOD is the most crucial antioxidant enzyme.[64] It catalyzes the dismutation of superoxide anion free radical (O_2^-) into molecular oxygen and hydrogen peroxide (H_2O_2), and decrease the O_2^- level which damages the cells at excessive concentration.[65] The decrease in SOD level indicates aging.[66] Studies have confirmed that ROS is an important cause of neuronal damage after cerebral hypoxia-ischemia.[67,68] LPO is a product of combination of the ROS and polyunsaturated fatty acids. Its significant increase causes serious damages to human cells, and to the structure and function of cell membrane.[69] LPO can also cause damage and fibrosis to the arterioles.[70] NO is a biological intercellular messenger or neurotransmitter.[71] It relaxes smooth muscle and inhibits platelet aggregation and cytotoxicity. NO derived from endothelial cells has anti-atherosclerotic effect and may be related to learning and memory.[68,72] Increase of NO has both protective and damaging effects.[73]

Previous systematic review suggested that acupuncture can improve cognitive function in animal studies,[53,74] and increase cerebral blood flow.[75] Acupuncture treatment can significantly increase SOD activity in brain and reduce brain tissue damage caused by free radical in rats.[31,76] It was found that the outcome on memory consolidation was closely correlated with the change of LPO and SOD in the brain. Higher SOD activity, lower LPO content and elevated SOD/LPO ratio in the brain were presented in rats which did well in the water maze test, showing significant effect of acupuncture in antagonizing oxygen stress.[77,78] Previous studies suggested that electroacupuncture can reduce the extent of lipid peroxidation in brains of rats with ischemic-reperfusion injury,[34] decrease NO content[79] and enhance SOD activity.[75,79] The present study shows that scalp electroacupuncture significantly increases the activity of SOD and decrease LPO and NO, indicating that it may enhance the body's ability to scavenge ROS and to oxidize, preventing it from causing further damage, and thus contribute to the patients recovery.

In this study, the continuation of increasing effect in the follow-up suggesting scalp electroacupuncture has persistent effect over the 4 weeks of post-treatment. The underlying mechanisms of scalp electroacupuncture on cognitive improvement may be partially attributable to its ability to enhance the body's capability to scavenge ROS and promote balance, which may contribute to the prolonged sustained effects of scalp electro-acupuncture. This may provide a new insight to explore the efficacy of its long term effects in future studies, and to develop a schedule if further treatment is required to reinforce the effect in long term control.

In conclusion, in combined treatment, scalp electroacupuncture works in parallel with Memantine and significantly increase the therapeutic effect in VaD with no significant adverse events. Scalp electroacupuncture may have the potential to serve as an option or alternative treatment for VaD. Scalp electroacupuncture may alleviate VaD symptoms through its antioxidative mechanism. The limitation of this study is it mainly focused on the short-term therapeutic effects. Further studies may involve comparisons with sham electroacupuncture. Future studies may evaluate the long-term therapeutic effects, as well as comparisons with other newer drug generation. In addition, the differences in outcome based on the site of lesions may also be explored.

Author contributions

Aixia Yue, Xiuqing Han and Bin Zhou designed the studies. Aixia Yue, Xiuqing Han, Enxia Mao, Guangling Wu, Junxiang Gao and Liping Huang performed the data collection and statistical analysis. Aixia Yue, Xiuqing Han, Enxia Mao and Bin Zhou conducted the data interpretation. Aixia Yue prepared the manuscript. Aixia Yue and Xiuqing Han did the literature search. All authors approved with the final manuscript.

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