

Neuroprotection against vascular dementia after acupuncture combined with donepezil hydrochloride: P300 event related potential

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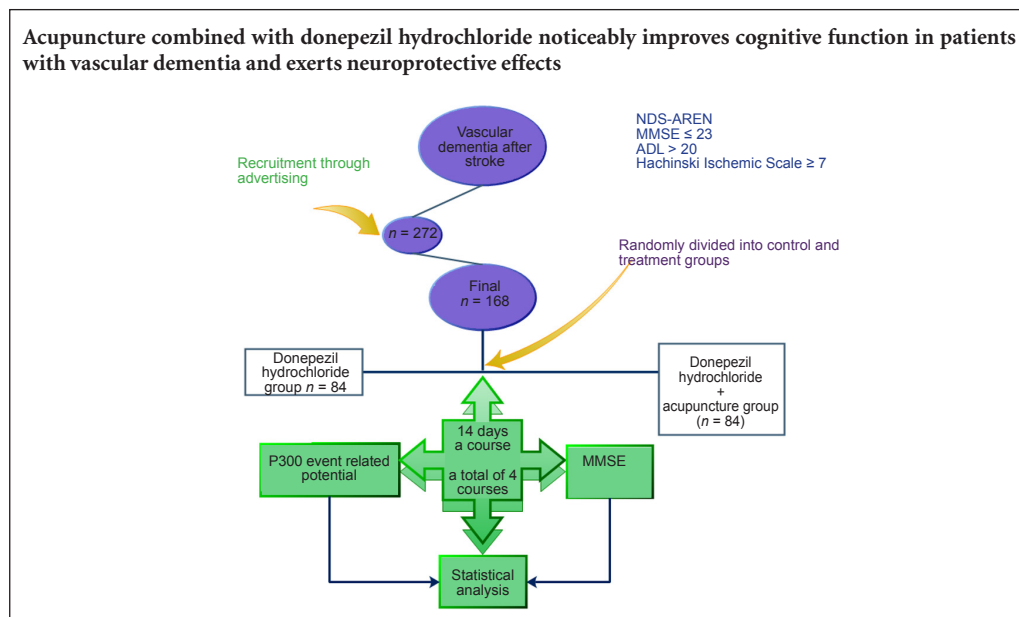
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Graphical Abstract



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Abstract

Acupuncture can be used to treat various nervous system diseases. Here, 168 vascular dementia patients were orally administered donepezil hydrochloride alone (5 mg/day, once a day for 56 days), or combined with acupuncture at *Shenting* (DU24), *Tianzhu* (BL10), *Sishencong* (Extra), *Yintang* (Extra), *Renzhong* (DU26), *Neiguan* (PC6), *Shenmen* (HT7), *Fengchi* (GB20), *Wangu* (GB12) and *Baihui* (DU20) (once a day for 56 days). Compared with donepezil hydrochloride alone, P300 event related potential latency was shorter with an increased amplitude in patients treated with donepezil hydrochloride and acupuncture. Mini-Mental State Examination score was also higher. Moreover, these differences in P300 latency were identified within different infarcted regions in patients treated with donepezil hydrochloride and acupuncture. These findings indicate that acupuncture combined with donepezil hydrochloride noticeably improves cognitive function in patients with vascular dementia, and exerts neuroprotective effects against vascular dementia.

Key Words: nerve regeneration; vascular dementia; acupuncture; donepezil hydrochloride; event related potential; cognitive function; infarct focus; neural regeneration

Introduction

Vascular dementia is strongly associated with cortical lesions, and particularly ischemia in the left cortex, thalamus and, hippocampus (Liu et al., 2014). Vascular dementia is also related to bilateral multiple cerebral infarction, ischemic

infarcts in major brain regions, and large-area brain damage (Gorelick, 1997). It is mainly induced by cerebrovascular disease, and therefore shares many common risk factors with stroke e.g., hypertension (Qiu et al., 2005; Paglieri et al., 2008), diabetes (Araki, 2010; Fei et al., 2013), hyperlipemia

(Purandare, 2009; Solomon et al., 2009), smoking (Mazzone et al., 2010; Gons et al., 2011), and drinking (Lobo et al., 2010; Weyerer et al., 2011). Medication for Alzheimer's disease and mild cognitive impairment is administered for vascular dementia, but the clinical significance of these medicines is uncertain (Dichgans et al., 2008). Complementary and alternative therapies such as acupuncture, exercise, and cognitive therapy have obtained certain therapeutic effects (Avila et al., 2004; Ding et al., 2006). Donepezil hydrochloride is a reversible, specific, long-acting acetylcholine esterase inhibitor that can effectively and selectively suppress acetylcholine degradation in the central nervous system, increase acetylcholine concentration in the synaptic cleft, and improve memory and mental status in vascular dementia patients (Meyer et al., 2002; Naik et al., 2009; Liu et al., 2012).

Acupuncture is one of the classical methods of traditional Chinese medicine, and can regulate learning and memory, the stress response, and emotion (Toriizuka et al., 1999; Yang et al., 2002; dos Santos Jr et al., 2008). Animal experiments show that acupuncture can treat Parkinson's disease by inhibiting dopamine decline (Kim et al., 2005), restore memory ability in rats with cerebral ischemia associated with diabetes (Jing et al., 2007, 2008), and improve cognitive dysfunction in age-accelerated mice (Cheng et al., 2008). Evidence-based medicine indicates that acupuncture combined with cognitive training effectively improves cognitive function, with the effects of acupuncture better than drug treatment alone (Zhou et al., 2013).

Sutton et al. (1965) first reported P300 event related potentials. The P300 event related potential defines electroencephalogram changes during cognitive processing (*e.g.*, attention, memory, and thinking) of objective events. Latency reflects the speed of event coding, classification, and identification, and objectively reflects the brain's cognitive and decision-making functions. Prolonged P300 latency indicates cognitive dysfunction induced by various encephalopathies. Amplitude and information processing are associated with the extent of effective resource mobilization. Decreased amplitude indicates reduced degree of effective resource mobilization during information processing (McCarthy and Donchin, 1981). Gaillard (1988) suggested that the P300 is the reaction advanced processing sensory endogenous component: it is a quantifiable electrophysiological indicator that objectively reflects the sensitive cognitive function, displays the degree of cognitive impairment, and monitors cognitive dysfunction (Gummow et al., 1986; Damulin et al., 2008). The Mini-Mental State Examination (MMSE) exhibits high specificity for measuring vascular dementia (Sun and Qin, 2011). Here, we used the P300 event related potential and MMSE to measure the protective effect of acupuncture combined with donepezil hydrochloride for treating vascular dementia after stroke.

Subjects and Methods

Subjects

A total of 272 stroke patients treated in the Department of Acupuncture and Moxibustion, Tianjin Nankai Hospital (China) and the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (China) from January to

December 2012 were recruited for this study. The diagnostic criteria were in accordance with the vascular dementia criteria formulated by the National Institute of Neurological Disease and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Rockwood et al., 2000). (1) Dementia and decline in cognitive capacity: memory impairment and one or more cognitive impairments (orientation, attention, language, visual-spatial function, executive function, motion control, and enforcement function); (2) cerebrovascular disease: focal neurological signs and relevant cerebrovascular disorders detected by CT/MRI; (3) dementia occurred within 3 months after stroke; (4) at least one or two of the following items: sudden cognitive decline or wave-like, ladder-like progression of cognitive impairment.

The inclusion criteria were: (1) vascular dementia criteria formulated by NINDS-AIREN; (2) MMSE score (Zhou et al., 2013) ≤ 23 ; (3) life and social dysfunction (not only induced by physical dysfunction), activities of daily living (Tian et al., 2000) > 20 ; (4) Hachinski Ischemic Scale (Tian et al., 2000) ≥ 7 ; (5) cognitive dysfunction appeared within 3 months after cerebrovascular disease; (6) mild or moderate National Institutes of Health Stroke Scale (NIHSS).

The exclusion criteria were: (1) patients exhibited unconsciousness, delirium, neurosis, severe aphasia, or obvious sensorimotor disorders, but did not show evidence of this on neuropsychological tests; (2) patients had systemic diseases that can cause memory or cognitive dysfunction, or other brain diseases such as Alzheimer's disease; (3) patients had taken antiepileptic drugs or antidepressants, before the stroke or dementia; (4) the patient or their family members did not agree to and did not complete the initial neuropsychological assessment; (5) patients were uncooperative and had poor compliance despite repeated explanations by the clinician; and (6) the patient's condition worsened during the study and emergency measures had to be taken. In addition, those (7) that dropped out; (8) did not receive regular treatment or did not have complete data; or (9) suffered from severe adverse events or complications and could not finish the study.

Of 272 vascular dementia patients, 168 patients finished the trial, including 106 males and 62 females. They were an average of 56 years old, ranging 45–55 years old (32 cases), 56–65 years old (78 cases), and 66–75 years old (58 cases). The disease course was between 3 months and 3 years (1.6 years on average). In addition, 95 cases had a history of hypertension, and 49 had a history of diabetes. According to CT or magnetic resonance angiography (MRA), the infarcted regions were the parietal lobe, frontal lobe, temporal lobe, occipital lobe, basal ganglia, internal capsule, and thalamus. Infarction was detected in the basal ganglia, internal capsule, and thalamus in 89 cases (unilateral in 49 cases, 55%; bilateral in 40 cases, 45%), in the parietal lobe and occipital lobe in 39 cases (unilateral in 20 cases, 51%; bilateral in 19 cases, 49%), and in the frontal lobe and temporal lobe in 40 cases (unilateral in 17 cases, 42%; bilateral in 23 cases, 58%).

All patients were equally and randomly divided into control and treatment groups. No significant differences in

Table 1 Baseline data of patients from both groups

Item	Control group (n = 84)	Treatment group (n = 84)	χ^2/t	P
Sex (n, male/female)	52/32	54/30	0.184	0.83
Age (year)	56±9	55±7	0.58	0.56
Schooling time (year)	6.33±2.48	6.47±1.96	-2.157	0.78
Course of disease (year)	3.2±0.9	2.9±0.7	0.45	0.67
NIHSS score	8.11±2.54	7.98±2.79	2.19	0.54
Barthel index	71.09±20.86	68.88±19.17	0.15	0.92
MMSE score	8.11±2.54	7.98±2.8	2.19	0.54
Activities of Daily Living Scale score	50.32±16.16	48.98±18.73	0.26	0.82
Hachinski Ischemic Scale score	11.62±1.93	11.70±1.71	1.23	0.72
Time of occurrence of cognitive dysfunction (month)	8.85±3.83	8.20±4.15	1.73	0.88

Data are expressed as the mean ± SD except for sex. Numeration data were compared using the chi-square test. Measurement data were compared using two-sample *t*-test after analysis of variance with a randomized block design. NIHSS: National Institutes of Health Stroke Scale; MMSE: Mini-Mental State Examination.

Table 2 Change in latency (ms) and amplitude (μV) of P300 event related potential after treatment with acupuncture and donepezil hydrochloride

	Control group	Treatment group
Before treatment		
Fz		
Latency	-6.5±4.1	-42.3±26.3
Amplitude	5.3±1.4	5.2±1.3
Cz		
Latency	421.6±13.4	422.1±11.5
Amplitude	5.9±2.4	5.7±2.7
Pz		
Latency	426.1±13.5	427.3±11.4
Amplitude	6.3±2.2	6.2±2.1
After treatment		
Fz		
Latency	392.1±15.6 [#]	361.7±11.7 ^{*#}
Amplitude	6.3±1.7	7.6±1.1 ^{*#}
Cz		
Latency	382.6±11.1 [#]	356.6±12.9 ^{*#}
Amplitude	6.2±2.2	7.8±2.1 ^{*#}
Pz		
Latency	387.1±15.5 [#]	354.6±14.8 ^{*#}
Amplitude	6.4±1.8	7.9±1.9 ^{*#}

Data are expressed as the mean ± SD with 84 patients in each group. Measurement data were compared using two-sample *t*-test after analysis of variance with a randomized block design. **P* < 0.05, vs. control group; #*P* < 0.05, vs. before treatment.

MMSE score, NIHSS score, Barthel index, and infarct region were identified between the two groups (*P* > 0.05), and the groups were comparable (Table 1).

Treatment with donepezil hydrochloride

Patients in the control and treatment groups orally took donepezil hydrochloride (trade name: Aricept; Eisai China Inc., Suzhou, Jiangsu Province, China; Approval No. H20050978): 5 mg/day, once a day, with 7 days as a course, for 8 courses. In accordance with the physical and laboratory examination results, drug treatments for improving circulation, regulating blood glucose, blood pressure, and blood lipids were executed.

Table 3 Change in MMSE score in vascular dementia patients after acupuncture combined with donepezil hydrochloride

Group	Before treatment	After treatment
Control	17.40±1.20	21.40±1.04 [#]
Treatment	17.36±1.97	25.59±1.07 ^{*##}

MMSE score ranges from 0 to 30. A high score indicates good cognitive function. Data are expressed as the mean ± SD with 84 patients in each group. Measurement data were compared using two-sample *t*-test after analysis of variance with a randomized block design. **P* < 0.05, vs. control group; #*P* < 0.05, ##*P* < 0.01, vs. before treatment. MMSE: Mini-Mental State Examination.

Acupuncture

Simultaneously, the patients in the treatment group were subjected to acupuncture at *Shenting* (DU24), *Tianzhu* (BL10) (bilateral), *Sishencong* (Extra), *Yintang* (Extra), *Renzhong* (DU26), *Neiguan* (PC6) (bilateral), *Shenmen* (HT7) (bilateral), *Fengchi* (GB20) (bilateral), *Wangu* (GB12) (bilateral), and *Baihui* (DU20). In accordance with Acupuncture and Moxibustion (Lu, 2002), patients in the supine position received acupuncture at *Fengchi* (GB20), *Wangu* (GB12), and *Tianzhu* (BL10) using a stainless steel needle (0.30 mm × 40 mm in diameter; Suzhou Medical Sino-foreign Joint Venture Suzhou Hua Tuo Medical Instruments Co., Ltd., Suzhou, China), with twirling at > 180 r/min for 1 minute until the patients felt soreness, numbness, and distention. Subsequently, the needle was inserted at *Baihui* (DU20) and *Shenting* (DU24) for 0.5–0.8 cun, and twirled at > 180 r/min for 1 minute until the local sensation of soreness, numbness, or distention was detected in the back of the head. The needle was then inserted at *Shenting* (DU24) and *Sishencong* (Extra) for 0.5 cun and twirled at > 180 r/min for 1 minute, and at *Yintang* (Extra) towards the nasal root for 0.3–0.5 cun with light twirling but no lifting or thrusting. The needle was obliquely inserted at *Renzhong* (DU26) towards the nasal septum for 0.3–0.5 cun, and the needling manipulation of heavy bird-peck used until the eyeballs were wet or tears appeared. *Neiguan* (PC6) and *Shenmen* (HT7) were perpendicularly manipulated for 0.5 cun using a mild reinforcing

Table 4 Change in latency (ms) and amplitude (μ V) in different infarcted regions of vascular dementia patients before and after acupuncture combined with donepezil hydrochloride

Group	n	Infarcted region	Latency			Amplitude		
			Altered value	t	P	Altered value	t	P
Control	46	Basal ganglia	-33.2 \pm 26.2	-8.222	0.000	0.1 \pm 0.7	0.997	0.324
	19	Frontal lobe, temporal lobe	-4.8 \pm 20.2	-1.044	0.310	0.1 \pm 0.5	-0.041	0.968
	19	Parietal lobe, occipital lobe	-79.9 \pm 31.0	-11.233	0.000	0.7 \pm 0.4	7.576	0.000
Treatment	43	Basal ganglia	-62.9 \pm 28.5	-13.961	0.000	2.3 \pm 1.1	13.823	0.000
	21	Frontal lobe, temporal lobe	-57.8 \pm 20.4	-13.014	0.000	2.2 \pm 1.0	10.319	0.000
	20	Parietal lobe, occipital lobe	-75.3 \pm 15.6	-22.019	0.000	2.4 \pm 0.7	14.765	0.000

Data are expressed as the mean \pm SD and compared using two-sample *t*-test after analysis of variance with a randomized block design.

and attenuating method combined with a twirling, lifting, and thrusting method for 1 minute. Acupuncture in the treatment group was performed once a day, with 14 days as a course, for a total of 4 courses. The control group did not undergo any acupuncture.

P300 event related potential measured using an electromyogram evoked potentiometer

The P300 event related potential was measured using a NDI-200 electromyogram evoked potentiometer (Dantec Dynamics A/S, Copenhagen, Denmark). The electrodes were placed on patients in the supine position in accordance with International 10-20 system (Zhou, 2001). Recording electrodes (G-) were placed on Fz, Cz, Pz, etc. Reference electrodes (G+) were placed on the ears (A1 or A2). A groundwire was placed on the forehead. Auditory stimulation was performed using an oddball sequence, which is a sequence of pure tone composed of target stimuli (target, T) with a frequency of 2,000 Hz, and non-target stimuli (non-target, NT) with a frequency of 1,000 Hz. The change in tone length ranged from 5 to 10 ms (50–100 ms in duration). The sound pressure level increased by 60 dB (on the basis of subjective hearing thresholds) with 2-second intervals.

MMSE

The MMSE determined the cognitive function of patients. MMSE is a 30-point questionnaire that contains seven categories: orientation to time, orientation to place, registration, attention calculation, recall, language, and repetition. The following cut-off levels are used to classify the severity of cognitive impairment: no cognitive impairment = 27–30; mild cognitive impairment = 21–26; moderate cognitive impairment = 10–20; and severe cognitive impairment = 0–10.

Statistical analysis

Data were processed using SPSS 17.0 software (SPSS, Chicago, IL, USA) and expressed as the mean \pm SD. Numeration data were compared between the two groups using the chi-square test. Measurement data were analyzed using analysis of variance with a randomized block design. Two-sample *t*-test was used if a normal distribution and homogenous variance were observed. The rank sum test was used if heterogeneity of variance was observed. A value of $P < 0.05$ was considered statistically significant.

Results

Improvement in P300 event related potential in vascular dementia patients after acupuncture combined with donepezil hydrochloride

In both groups after treatment, the P300 latency shortened while the amplitude increased at different sites (Fz, Cz, and Pz). However, the latency was shorter and amplitude greater in the treatment group compared with the control group ($P < 0.05$). In the treatment group, no significant difference in latency and amplitude was detected among the three sites (Fz, Cz, and Pz) ($P > 0.05$; Table 2).

Highly increased MMSE score in vascular dementia patients after acupuncture combined with donepezil hydrochloride

MMSE score was examined in the treatment and control groups after treatment ($P < 0.01$ or $P < 0.05$). MMSE score was significantly higher in the treatment group than the control group ($P < 0.05$; Table 3).

Change in P300 event related potential in different infarcted regions of vascular dementia patients before and after acupuncture combined with donepezil hydrochloride

In the treatment group, the P300 latency was significantly shortened and the amplitude significantly prolonged ($P < 0.01$). No significant difference in latency and amplitude was detected in 19 patients with frontal lobe and temporal lobe infarction in the control group after treatment ($P > 0.05$). In addition, the latency was shortened ($P < 0.01$), but amplitude not significantly altered in 46 patients with basal ganglia infarction in the control group after treatment ($P > 0.05$). However, the amplitude was significantly increased and latency significantly shortened in 19 patients with parietal lobe and occipital lobe infarction in the control group ($P < 0.01$; Table 4).

Discussion

Cognitive dysfunction mainly presents with a prolonged P300 latency and decreased amplitude in stroke patients (Suzuki and Hoshiyama, 2011). However, our results show no significant difference in latency and amplitude at Fz, Cz, and Pz before and after treatment in the treatment group. The P300 event related potential reflects brain function. Xu et al. (2010) confirmed that acetylcholine, serotonin, and norepinephrine can regulate P300 latency and amplitude.

Furthermore, acupuncture regulates cholinesterase inhibitors, serotonin, and noradrenaline after dementia.

In conclusion, acupuncture combined with donepezil hydrochloride effectively improves cognitive function in vascular dementia patients. Thus, our combined therapy has noticeable advantages in improving cognitive function and protecting against vascular dementia compared with donepezil hydrochloride alone.

Author contributions: QL provided data, ensured the integrity of the data, and participated in study conception and design. XJW participated in data analysis, and paper writing. PL provided technical support. ZCZ and RX were in charge of paper authorization. All authors approved the final version of the paper.

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