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CLINICAL STUDY

Alzheimer's disease treated with combined therapy based on nourishing marrow and reinforcing *Qi*

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Abstract

OBJECTIVE: To study the efficacy and safety of combined Traditional Chinese Medicine (TCM) therapy based on nourishing marrow to improve intellect and reinforcing *Qi* to activate bloodon mild to moderate Alzheimer's disease (AD).

METHODS: Sixty-six patients with AD, whoseMini-Mental State Examination (MMSE) score were from 10-24, were randomized equally into an intervention group and a control group. The control group was given Aricept (5 mg, once daily). The intervention group was further divided into *Yang-Qi* deficiency (n = 18) and of *Yin-Qi* deficiency (n = 15) subgroups. Patients in the *Yang-Qi* deficiency group were intravenously administered Shenfu injection, 60 mL, and deproteinized calf blood injection (DCBI), 1.2 g, once daily. The *Yin-Qi* deficiency group was given Shenmai injection, 60 mL, and DCBI, 1.2 g, once daily. Each course lasted 21 days.

RESULTS: Compared with the control group and with pre-treatment in the same group, MMSE, clinical dementia rating, and activities of daily living scale scores in the intervention group were significantly improved (all $P < 0.05$). These metrics mildly improved in the control group compared with before treatment ($P > 0.05$). No adverse effects were observed in any group during treatment.

CONCLUSION: We found that combined TCM therapy is effective and safe for managing mild to moderate AD.

Key words: Alzheimer disease; Combined modality therapy; Donepezil; Deproteinized calf blood injection

INTRODUCTION

Alzheimer's disease (AD) is a progressive degenerative disease of the nervous system, which manifests as declined cognitive function, mental behavior, and ability to complete the activities of daily life. The prevalence of AD is increasing as the population ages, placing aheavy burden on families and society. Aricept is effective in the treatment of AD by inhibiting the degradation of acetylcholine in the brain, which increases the concentration of acetylcholine in the cerebral cortex.[1] We aimed to use a combined Traditional Chinese Medicine (TCM) treatment, based on nourishing marrow to improve intellect and reinforcing *Qi* to activate

blood, to treat mild to moderate AD. We compared this TCM treatment with that of conventional Aricept.

MATERIALS AND METHODS

Diagnosis criteria

AD was diagnosed according to the American Diagnostic and Statistical Manualof Mental Disordersand the standarddiagnosis criteria of the National Institute of Neurological Disorders and Stroke.[2]

Inclusion and exclusion criteria

Patients were included if they: (a) met the diagnostic criteria; (b) were ≥55 years old; (c) had a MMSE score from 10-24; (d) were able to see, hear, speak to accomplish each measurement; (e) agreed to the treatment and signed their informed consent. This treatment was approvedby the Medical Ethics Committee of First AffiliatedHospital of Zhongshan University.

The exclusion criteria included: (a) dementia caused by other disease, such as vascular disease, brain trauma, encephalitis, Parkinson's disease and other problems; (b) patients who received prior treatment for AD; (c) patients who had other severe cardiovascular, hepatic, or renal disease.

Patient grouping

Sixty-six AD patients were treated in the Department of Neurology or Traditional Chinese medicine (TCM) of the First Affiliated Hospital of Sun Yet-sun University, from 2007 to 2013. Patients were randomized equally into an intervention group and control group using the software SPSS 12.0 (SPSS, Chicago, IL, USA). The intervention group was further divided into the *Yang-Qi* deficiency (n = 18) and *Yin-Qi* deficiency subgroups (n = 15), as previously described.[3] Study subjects were blinded to treatments,while resultsevaluators were unblinded.

There were no significant differences among groups in terms of age, gender, disease course, pathogenic conditions, including the mini-mental state examination (MMSE) scores, clinical dementia rating (CDR) scores,activities of daily living scale (ADL) scores, or years of education before treatment (all $P > 0.05$) (Table 1).

Treatment

Patients in the control group were orally administered 5 mg of Aricept (Eisai pharmaceutical [Suzhou] Co., Ltd.,batch No. H20050978, Suzhou, China) once a night.Patients in the *Yang-Qi* deficiency subgroup were intravenously administered Shenfu injection (Ya'an 999 Pharmaceutical Co., Ltd., Ya'an, China; batch No. Z51020664), which is composed of Hongshen (*Radix Ginseng Rubra*) and Fuzi (*Radix Aconiti Lateralis Preparata*), 60 mL *via* intravenous drip, once daily. The *Yang-Qi* deficiency subgroup was also given deproteinized calf blood injection, (DCBI, Jinzhou Aohong Pharmaceutical Co., Ltd., Jinzhou, China; batch No. H20010762; one 10 mL ampoule contains 0.4 g) 1.2 g, intravenous drip, once daily. The *Yin-Qi* deficiency subgroup was intravenously administered 60 mL of Shenmai injection (Ya'an 999 Pharmaceutical Co., Ltd., batch No. Z51021879), which is composed of Hongshen (*Radix Ginseng Rubra*) and Maidong (*Radix Ophiopogonis Japonici*) once daily, plus 1.2 g of DCBI once daily *via* intravenous drip.The treatment course for both groups was 21 days.

Observation indicators and methods

Before and after treatment, each AD patient was evaluated with: (a) MMSE[4] to assess cognitive function; (b) CDR[4]to assess degree of dementia; and (c) ADL[4] to assess activities of daily life.

Safety evaluation

Before and after treatment, the following were assessed: (a) neurological examination; (b) vital signs; (c) laboratory examination, including blood, urine, and stool panels; liver and kidney function tests; and blood glucose and electrolytes; and (d) electrocardiogram and chest X-ray.

Statistical analysis

Statistical analyses were performed with SPSS (Chicago, IL, USA). Data are presented as mean ± standard deviation ($\bar{x} \pm s$). Measurement data were compared using t-test. $P < 0.05$ is considered statistically significant.

RESULTS

Cognitive function

From before to after treatment, MMSE scores increased from 16.8 ± 4.3 to 27.7 ± 2.0 in the intervention group ($P < 0.05$), and 15.2 ± 4.7 to 17.7 ± 2.4 in the control group ($P > 0.05$). The MMSE score increasedmore significantly in the intervention group than that in the control group ($P < 0.05$) (Table 2).

Dementia level score

After treatment, the CDR scores decreased significantly in the intervention group ($P < 0.05$), while the control group scores decreased mildly compared to before treatment ($P > 0.05$). The decrease in the CDR score was significantly greater in the intervention group than that in the control group ($P < 0.05$) (Table 2).

Self-care ability in daily living

After treatment, the ADL scores significantly decreased in the intervention group ($P < 0.05$), while the control group scores were decreased mildly compared with before treatment ($P > 0.05$). The decrease in the ADL score was significantly greater in the intervention group than that in the control group ($P < 0.05$) (Table 2).

Table 1 Alzheimer's patient information in both treatment groups ($\bar{x} \pm s$)

Group	*n*	Male (*n*)	Female (*n*)	MMSE	CDR	ADLS	Educated year	Age (years)	Course of disease (years)
Intervention	33	20	13	16.8±4.3	1.5±0.4	46.2±7.9	9.1±5.3	67.9±13.3	3.9±2.9
Control	33	18	15	15.2±4.7	1.6±0.5	47.3±6.1	8.3±4.7	69.2±15.7	3.7±3.1

Notes: the control group was orally administered Aricept. The intervention group was further divided into the *Yang-Qi* deficiency (*n* = 18) and *Yin-Qi* deficiency subgroups (*n* = 15). Patients in the *Yang-Qi* deficiency subgroup were intravenously administered Shenfu injectionplus a deproteinized calf blood injection. The *Yin-Qi* deficiency subgroup was intravenously administered Shenmai injection plus a deproteinized calf blood injection. MMSE: mini-mental state examination; CDR: clinical dementia rating; ADLS: activities of daily living scale.

Table 2 Changes in rating scales of Alzheimer's patients before and after treatment ($\bar{x} \pm s$)

Group	*n*	MMSE		CDR		ADLS	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Intervention	33	16.8±4.3	27.7±2.0[ab]	1.5±0.4	0.8±0.3[ab]	46.2±7.9	29.5±7.6[ab]
Control	33	15.2±4.7	17.7±2.4	1.6±0.5	1.4±0.4	47.3±6.1	41.5±6.3

Notes: the control group was orally administered Aricept. The intervention group was further divided into the *Yang-Qi* deficiency (*n* = 18) and *Yin-Qi* deficiency subgroups (*n* = 15). Patients in the *Yang-Qi* deficiency subgroup were intravenously administered Shenfu injectionplus a deproteinized calf blood injection. The *Yin-Qi* deficiency subgroup was intravenously administered Shenmai injection plus a deproteinized calf blood injection.MMSE: mini-mental state examination; CDR: clinical dementia rating; ADLS: activities of daily living scale. [a]$P < 0.05$, compared with the pre-treatment in the same group; [b]$P < 0.05$, compared with the control group after treatment.

In the intervention group, drugs were withdrawn after 3 weeks of treatment, and there was no noticeable symptom rebounding after 12 weeks of follow-up. The control group maintained administration of Aricept.

Adverse reactions

No abnormal changes were found in the laboratory examination in either group. No abnormal changes were found in the neurologic examination, vital signs, electrocardiogram, or chest X-ray in either group. During treatment, four patients in the intervention group experienced mild dizziness, but symptoms improved after slowing down the speed of medicine infusion. In the control group, three patients suffered from excitation and insomnia, but changing the time of Aricept administration from night to morning improved the symptoms. No adverse reactions that impacted treatment were observed.

DISCUSSION

AD is a neurodegenerative disorder of the central nervous system. The clinical manifestation of AD is thought to be caused by acetylcholine dysfunction in the neurons of the cerebral cortex. AD symptoms result from decreased choline acetyltransferase activity and therefore reduced acetylcholine concentration in the brain.[5] Aricept is a specific inhibitor of acetylcholinesterase, and inhibition of acetylcholine degradation in the central system has been shown to improve cognitive dysfunction. While acetylcholinesterase inhibitors can improve cognitive function in patients with AD after 4 weeks, it must be taken continuously to maintain its effect. We found that Aricept did not improve the manifestation of AD after 21 days, which is consistent with other reports.[4] However, the combined TCM intervention group had significantly improved MMSE, CDR, and ADL scores compared with before treatment and compared with the control group (all $P < 0.05$).

According to TCM, the fundamental etiology and pathogenesis of AD is Kidney deficiency. Congestion and muddy phlegm are important factors for the onset of AD. *Yi Xue Xin Wu* [6] stated that "intellect is based on kidney. Kidney deficiency leads to mental retardation," and "insufficiency of kidney essence leads to brain marrow dystrophy, and dementia." AD is considered to lead to stagnant blood and muddy phlegm accumulation because of the deficiency of *Qi* and blood, and dysfunction of viscera. *Ling Shu Ying Wei Sheng Hui* [7]stated that"*Qi* and blood of the elderly is deficient.Theirmuscles are withered and consumed, *Qi*-passages arestagnant, nutrient *Qi* is declined, and defense *Qi* is subjugated inwardly." Therefore, AD treatment should include the pathogenic factors of kidney deficiency, marrow vacancy, and blood stagnancy because of *Qi* deficiency. Moreover, treatment should focus on invigorating the kidney to consolidate semen, nourishing the cerebral marrow to improve intellect, and reinforcing *Qi* to activate blood.

When treating AD in TCM, reinforcing kidney is emphasized. TCM treatment aims to increase essence and marrow to nourish the brain. DCBI has been shown tosignificantly improve damaged brain cells, and can provide protection and nutrition, and restore cerebral neurons via multiple targets.[8-12] These effects from DCBI are similar to nourishing marrow to improve intellect in TCM.

DCBI can activate aerobic metabolism, and increase the production of ATP in the mitochondria, which increases the use of oxygen in neurons. DCBI also contains phosphoinositide oligosaccharides, which can stop nitric oxide (NO) synthesis by inhibiting NO synthase. Therefore, DCBI blocks the NO-mediated ischemic cascade and prevents cell damage.[13] We found that DCBI combined with Shenmai or Shenfu was very effective for AD. After 21 days of treatment, the MMSE, CDR, and ADL scores in the intervention group were all improved (all $P < 0.05$). The combined therapy may repair the neuronal damage that causes AD at the molecular and cellular levels.

Hongshen (*Radix Ginseng Rubra*) is the main ingredient in the Shenmai and Shenfu injections. The main bioactive compounds found in Hongshen (*Radix Ginseng Rubra*) are ginseng saponins, which have neurotrophic functions and can enhance brain energy metabolism. They also canreduce NO production, prevent free radical damage, protect neurons, increase synaptic neurotransmitter uptake, and significantly inhibit acetylcholinesterase. Moreover, ginseng saponins can regulate immune function and enhance memory in the central nervous system. Ginsenosides Rb1 and Rg1, which are ginseng saponins, can increase the density of muscarinic acetylcholine receptors. By inhibiting the cAMP-dependent phosphodiesterase in the hippocampus of aged rats, ginseng saponins can also reduce the concentration of intracellular synaptic calcium ions, and resist excitatory amino acid neurotoxicity to protect nerve cells. Therefore, Hongshen (*Radix Ginseng Rubra*) has possible anti-AD effects.[14]

In TCM, Hongshen (*Radix Ginseng Rubra*) nourishes the brain and reinforces intelligence. It can also reinforce *Qi* to activate and improve blood circulation, which helps other drugs reach the lesions. *Ben Cao Jing Shu*, a classic Chinese treatise for description of the properties and functions of Traditional Chinese Medicine,[15] stated that "Hongshen (*Radix Ginseng Rubra*) can tonify genuine *Yang Qi* of the five *Zang*-organs and is effective in patients suffering from genuine *Yang* exhaustion and kidney *Qi* deficiency."

According to TCM theories, *Qi* deficiency is divided into *Yang-Qi* deficiency and *Yin-Qi* deficiency.[3] Patients with *Yang-Qi* deficiency often have cold limbs, the need to urinate frequently at night, little desire to talk, shortness of breath, devitalized essence-spirit, a pale and fat tongue with scalloped edges, glossy white or slimy white tongue fur, and a deep, fine, and weak pulse or floating, large, and weak pulse. Patients with *Yin-Qi* deficiency often have a pale white complexion, lassitude, palpitation, reduced sleep, forgetfulness, vexation, a dry mouth, tinnitus, backache, limp knees, red tongue with scanty fur, and a fine, string-like pulse. Treatment based on syndrome differentiation results in the best treatment effect.

Shenfu injection is prepared from Hongshen (*Radix Ginseng Rubra*) and Fuzi (*Radix Aconiti Lateralis Preparata*). Hongshen (*Radix Ginseng Rubra*) can tonify *Qi*, prevent exhaustion, and nourish *Qi* to vitalize the blood. Fuzi (*Radix Aconiti Lateralis Preparata*) can assist *Yang* with pungent warmth and free the twelve channels. The combination of the two medicines can boost *Qi*, warm *Yang*, move blood, and free channels. Shenfu injection contains ginsenosides, water-soluble alkaloids, and many other biologically active components. The injection can improve brain energy metabolism by increasing cerebral blood flow and slowing down the damage of cellular structures by preventing intracellular calcium overload.[16] Fuzi (*Radix Aconiti Lateralis Preparata*) has glucocorticoid-like anti-inflammatory effects. Compounds found in the herb can dilate brain arteries and improve brain hypoxia *via* anti-coagulation and anti-platelet aggregation effects. The drug can also restore brain neuron injury.[17]

Shengmai injection is prepared from Hongshen (*Radix Ginseng Rubra*) and Maidong (*Radix Ophiopogonis Japonici*). Maidong (*Radix Ophiopogonis Japonici*) has a slightly cold nature that nourishes *Yin* and boosts *Qi*. Shengmai injection can boost *Qi*, nourish blood and *Yin*, and vitalize liquids.[18]

The pattern type in TCM provides a basis for TCM treatment and does not affect treatment efficacy evaluations.[3] Therefore, we did not distinguish or analyze effectiveness between the TCM pattern types.

Our TCM-based protocol aims to manage AD by nourishing marrow to improve intellect and reinforcing *Qi* to activate blood. DCBI combined with Shenfu or Shenmai has definitive effects on improving the symptoms of mild to moderate AD in terms of cognitive function, dementia, and self-care ability in daily living. During treatment, no adverse effects that affected the treatment were observed.

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