

Dengzhan shengmai capsule combined with donepezil hydrochloride in the treatment of Alzheimer's disease: preliminary findings, randomized and controlled clinical trial

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SUMMARY

OBJECTIVE: To observe the effects of Dengzhan Shengmai capsule combined with donepezil hydrochloride on cognitive function, daily living ability, and safety in patients with Alzheimer's disease.

METHODS: A total of 294 patients with Alzheimer's disease were randomly divided into a treatment group and a control group, 147 cases each group. The control group was given oral donepezil hydrochloride 5 mg once a day, and the treatment group was given oral Dengzhan Shengmai capsule 0.36 g three times a day, based on the control group.

RESULTS: At 3 and 6 months of treatment, the ADAS-cog score of the treatment group was 48.69 ± 6.23 and 44.24 ± 5.53 ; for the control group, 45.48 ± 5.94 and 41.57 ± 5.10 . The difference between the two groups is statistically significant ($p < 0.05$). At 3 and 6 months of treatment, the NO level in the treatment group was (46.28 ± 6.68) $\mu\text{mol/l}$, (43.55 ± 7.92) $\mu\text{mol/l}$, and the control group was (42.95 ± 7.92) $\mu\text{mol/l}$, (38.89 ± 5.93) $\mu\text{mol/l}$. The differences between both groups were statistically significant ($p < 0.05$). At 3 and 6 months of treatment, ET levels in the treatment group were (156.08 ± 17.39) ng/l , (144.91 ± 17.60) ng/l , and the control group was (150.48 ± 22.94) ng/l , (135.04 ± 10.08) ng/l . Correlation analysis showed that ADAS-cog score was negatively correlated with NO and ET ($p < 0.001$).

CONCLUSIONS: Dengzhan Shengmai capsule combined with donepezil hydrochloride can improve cognitive function and the living capacity of patients with Alzheimer's disease, reduce the production of neurotoxic substances NO and ET, and provide higher safety.

KEYWORDS: Alzheimer's disease. Donepezil. Flavonoids. Medicine, traditional Chinese.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative condition of the central nervous system (CNS) characterized by progressive cognitive and behavioral impairment in older adults and pre-niles¹. In China, the incidence of AD in people over 65 years of age is 3–7%, resulting in a total of 6–8 million AD patients in China². Recently, studies have shown that oxidative stress, endothelial cell damage, and mitochondrial dysfunction are

involved in the pathogenesis of AD. Donepezil hydrochloride is currently the only drug supported by clinical evidence for being effective in the treatment of AD. Dengzhan Shengmai Capsule is a traditional Chinese medicine that contains flavonoids, which regulate vascular endothelial cells and protect mitochondria. Recently, the efficacy of Dengzhan Shengmai Capsule combined with donepezil hydrochloride in the treatment of AD has been confirmed in our department.

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METHODS

Clinical information

A total of 294 patients with AD who were treated in the neurology clinics of our hospital or as inpatients, from July 2015 to November 2017, were selected for the study. Patients were randomly assigned to either the treatment or control groups. The treatment group consisted of 147 cases, of which 26 were male and 23 were female. Patients were aged 67–84, with an average age of 70.93 ± 5.47 years. The control group consisted of 25 males and 24 females, aged between 66–81, with an average age of 70.48 ± 6.56 years.

The inclusion criteria for the study were patients who meet the diagnostic criteria for AD³; patients >60 years of age; patients who could complete the study; and patients with brain CT or MRI who did not show signs of cerebral hemorrhage, cerebral infarction, and intracranial lesions. The exclusion criteria for the study were patients with other types of dementia, such as vascular dementia; patients with advanced Parkinson's disease; patients with intracranial infections, schizophrenia, or depression; patients with severe heart, liver, lung, and kidney dysfunction; patients previously treated for dementia; and patients allergic to Dengzhan Shengmai Capsule or donepezil hydrochloride.

The study was approved by the hospital ethics committee and all subjects were recruited under written informed consent. The Ethical Approval Number is 2012-10-003. No significant difference in the general patient characteristics was observed between both groups ($p > 0.05$), as summarized in Table 1.

Table 1. Comparison of clinical data in two groups.

Item	Treatment (n=147)	Control (n=147)
Age (year)	69.12±5.28	69.31±5.41*
Sex (M/F)	75/72	74/73*
HR (Time/min)	78.52±15.18	71.48±12.30*
Weight (kg)	64.28±6.78	65.40±7.88*
BMI (kg/m ²)	22.40±1.92	22.89±2.06*
SBP (mmHg)	120.71±14.99	119.14±14.71*
DBP (mmHg)	74.42±10.51	73.57±12.25*
Education (year)	7.14±2.38	7.10±2.28*
Combined disease (n%)		
Hyperlipidemia	23(15.64)	25 (17.00)*
Hypertension	17(11.56)	16 (9.41)*
Diabetes	10(6.80)	11 (7.48)*

HR: heart rate; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Compared to the treatment group, * $p > 0.05$.

Treatment method

Patients in the control group received 5 mg of donepezil hydrochloride orally once a day (specification 5 mg/piece, Eisai (China) Pharmaceutical Co., Ltd., approval number: Sinopharm standard H20050978). The treatment group was based on the control group, who received 0.36 g Dengzhan Shengmai Capsule three times a day (specification: 0.18 g/capsule, Yunnan Biological Valley Dengzhanhua Pharmaceutical Co., Ltd., approval number: Sinopharm standard word H20054470). Patients in both groups were treated over six months.

Observation indicators

Cognitive function was measured with cognitive function scoring. A daily living capacity score and the adverse drug reactions of the two groups of patients before treatment and at three and six months of treatment were recorded. Cognitive function scores were assessed using the ADAS-cog scale, including structure, language, immediate recall and recognition of words, orientation, and the use of ideas. The total possible score was 70 points, in which a higher score indicated worse cognitive function. The daily living capacity score was assessed using the AD Collaborative Research Daily Ability Scale (ADCS-ADL) that consists of 19 ADCS-ADL scales with a total score of 54 points. A higher score indicated a better daily living capacity.

Fasting peripheral venous blood was collected in the early morning before treatment, three months and six months after treatment; the serum levels of nitric oxide and endothelin were measured using enzyme-linked immunosorbent assay after serum isolation. Nitric oxide (NO) detection kit was provided by the American Adlitteram Diagnostic Laboratorues Company (batch number: X01872); endothelin (ET) detection kit was provided by Shanghai Hengyuan Biotechnology Company (batch number: 20150219).

Statistical analysis

Statistical analysis was performed using SPSS17.0 software. Measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm s$), comparison between groups was tested by t test; count data were compared by percentage (%), and comparison between groups was tested by chi-square (χ^2) test. $p < 0.05$ indicates a statistically significant difference.

RESULTS

Clinical data

All participants from the treatment and control groups completed the study and were included in the analysis. The demographic characteristics, comorbid diseases, and laboratory tests

are shown in Table 1. All variables were not significantly different between the two groups. ($p>0.05$). There was no significant difference in ADAS-cog, ADCS-ADL scores between the two groups of patients before treatment ($p>0.05$). The scores of ADAS-cog and ADCS-ADL in the treatment group at three months and six months after treatment were significantly different from those in the control group ($p<0.05$) (Table 2). There was no significant difference in the levels of NO and ET between the two groups of patients before treatment ($p>0.05$).

The differences between the treatment group and the control group at three and six months after treatment were statistically significant ($p<0.05$) (Table 3). The Spearman correlation method was used to analyze the correlation between ADAS-cog scores, and NO and ET levels in the treatment group. The results showed that ADAS-cog scores were significantly negatively correlated with NO and ET levels ($r=-0.887, -0.608, p<0.05$). During the six months of treatment, adverse drug reactions in the treatment group were as follows: three cases

Table 2. Comparison of Alzheimer's disease assessment scale-cognitive scores and Alzheimer's disease cooperative study – activities of daily living between the two groups ($\bar{x}\pm s$).

Item	Treatment (n=147)			Control (n=147)		
	Before treatment	3 months	6 months	Before treatment	3 months	6 months
ADAS-cog	51.17±8.67	45.48±5.94	41.57±5.10	52.04±9.16*	48.69±6.23#	44.24±5.53#
ADCS-ADL	39.02±5.28	43.91±4.25	46.57±3.86	38.89±5.13*	40.77±4.44#	42.46±5.18#

ADAS-cog: Alzheimer's disease assessment scale-cognitive; ADCS-ADL: Alzheimer's disease cooperative study – activities of daily living. Compared to the treatment group, * $p>0.05$, # $p<0.05$

Table 3. Comparison of no and et levels between two groups($\bar{x}\pm s$).

Item	Treatment (n=147)			Control (n=147)		
	Before treatment	3 months	6 months	Before treatment	3 months	6 months
NO (umol/l)	49.25±10.97	42.95±7.92	38.89±5.93	49.17±9.18*	46.28±6.68#	43.55±7.92#
ET (ng/l)	158.59±24.13	150.48±22.94	135.04±10.08	159.95±20.16*	156.08±17.39#	144.91±17.60#

Compared to the control group, * $p>0.05$, # $p<0.05$.

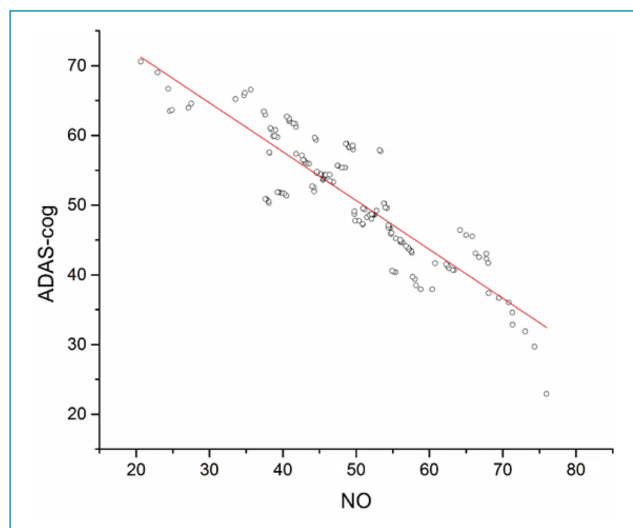


Figure 1. Correlation analysis between Alzheimer's disease assessment scale-cognitive with Nitric oxide.

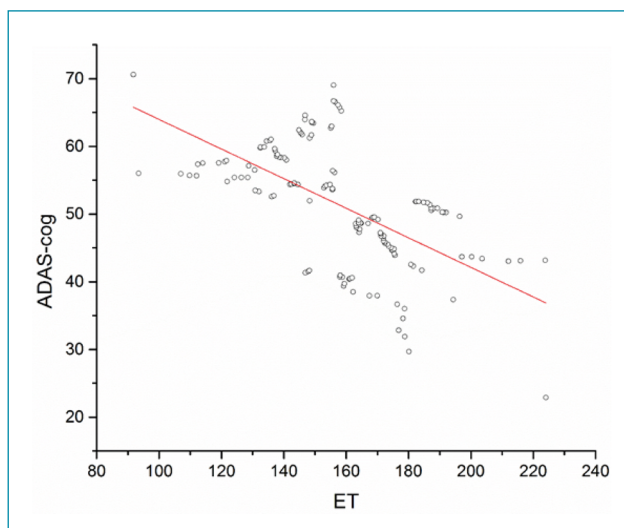


Figure 2. Correlation analysis between Alzheimer's disease assessment scale-cognitive with Endothelin.

of nausea, two cases of insomnia, one case of headache, two cases of dizziness, one case of diarrhea, one case of rash, and dynamic monitoring of liver and kidney function, and electrocardiogram during the whole course showed no significant dynamic changes. Adverse drug reactions in the control group were as follows: two cases of nausea, three cases of insomnia, two cases of rash, one case of fatigue, and dynamic monitoring of liver and kidney function, and electrocardiogram during the whole course showed no significant dynamic changes. The incidence of adverse reactions in the treatment group and the control group was 6.81 and 5.44%, and the difference was not statistically significant ($p>0.05$).

DISCUSSION

AD is one of the most common chronic diseases in older people and is a major global public health concern. Since ancient times, traditional Chinese medicine has provided a detailed description of the disease. “Qianjin Yaofang” refers to the disease as a person with more than 50 years of age and dysfunction. “Laziness” and “Medical Forest Corrects Errors” describes the fact that “in children with no memory, the brain is not full, and in those with advanced memory, the brain gradually declines”.

Traditional Chinese medicine believes that the pathogenesis of AD involves “the lack of marrow sea and the use of a magic machine”. Its pathological properties have been described as “the time when the essence is true, the essence is yin essence, qi and blood deficiency, and the essence is Qi, fire, Sputum and stasis are blocked in the brain”. Therefore, “empty marrow sea, liver and kidney deficiency, heart and liver fire, qi stagnation and blood stasis, phlegm and turbidity” are the root causes of this disease⁴.

For the treatment of AD, the principles of traditional Chinese medicine are Kaiyuzhutan, Huoxuetongqiao, Pingganxiuehuo treatment of its symptoms, tonicity, righteousness, and filling the brain. At present, the treatment of AD uses drugs. Donepezil hydrochloride in Western medicine can reversibly inhibit the hydrolysis of acetylcholine by acetylcholinesterase and can be used in the treatment of mild, moderate, and severe AD^{5,6}. However, Western medicine often has more toxic side-effects compared to traditional Chinese medicine.

Dengzhan Shengmai Capsule is a traditional Chinese medicine preparation developed from several precious medicinal materials, such as Dengzhan Asarum, Ginseng, Schisandra, and Ophiopogon. The main component of the drug is Erigeron breviscapus, which is a flavonoid compound extracted from Erigeron breviscapus⁷. Schisandrol contained in Schisandra chinensis has been shown to have a protective effect on synapses and

mitochondria. Also, basic research has shown that Schisandrolone can significantly improve the learning ability of AD model rats⁸.

In this study, through the results of a randomized controlled clinical trial, we found that donepezil hydrochloride combined with the Dengzhan Shengmai Capsule significantly improved ADAS-cog, ADCS-ADL scores in patients with AD compared to donepezil hydrochloride alone.

There are currently many hypotheses concerning the pathogenesis of AD in Western medicine. The β -amyloid waterfall hypothesis suggests that imbalance in the production and clearance of $A\beta$ is the initial event leading to neuronal degeneration and dementia⁹. The tau protein theory believes that over-phosphorylation of the tau protein affects the stability of neuron skeleton tubulin leading to the formation of neuron fiber tangles that disrupt the normal functions of neurons and synapses¹⁰. These two theories have been confirmed based on the histopathological manifestations of AD, which include neuritic and neuro-inflammatory plaques formed by beta-amyloid deposition, and neurofibrillary tangles formed by hyperphosphorylated tau protein.

Recently, oxidative stress has been implicated in the onset of AD¹¹. Oxidative stress refers to the imbalance between the production and removal of oxygen free radicals in the body, resulting in the accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Nitric oxide (NO) is one of the common species in the RNS family. Studies have shown that NO can regulate the synaptic plasticity of neurons and that excessive increases in NO can directly damage neuronal cells¹². NO can also activate multiple intracellular signals to enhance the activity of P53, resulting in increased expression of pro-apoptotic caspases to promote neuronal cell apoptosis¹³.

In this study, we showed that the expression of NO in the peripheral serum of patients with AD significantly increased. Correlation analysis showed that NO was negatively correlated with the ADS-cog score, which confirmed that NO is involved in the pathogenesis of AD^{10,14,15}. Brain tissue hypoperfusion and microvascular endothelial changes have also been linked to the pathogenesis of AD^{16,17}. Endothelin-1 (ET-1) is currently the strongest known vasoconstrictor. A large amount of ET-1 production can cause intracranial vasoconstriction, resulting in chronic cerebral blood flow insufficiency, thus causing vascular and mitochondrial dysfunction, and increased production of ROS, leading to AD^{17,18}.

We showed that the level of ET-1 in AD patients was significantly higher than that in the normal population. Correlation analysis showed that ET-1 was negatively correlated with the ADAS-cog score, suggesting that ET-1 is involved in the pathogenesis of AD. Moreover, the levels of NO and ET-1 in the

experimental group were significantly lower than in the control group, in March and June, after treatment. These data suggest that Dengzhan Shengmai Capsules can reduce ET-1 by relaxing intracranial blood vessels in AD patients. The release of ET-1 can also protect mitochondria by reducing the production of the oxidative stress product NO.

CONCLUSIONS

Dengzhan Shengmai Capsule combined with donepezil hydrochloride can be used to effectively treat AD by significantly

improving the ADAS-cog scores of AD patients. Reduced levels of neurotoxic substances (NO and ET) were also observed; patients showed an improved quality of life when compared to AD patients without adverse drug reactions.

AUTHORS' CONTRIBUTIONS

PH: Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **XH:** Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MX:** Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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