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Original Research

Effects of Dengzhan Shengmai Capsule combined with butylphthalide soft capsule on oxidative stress indexes and serum Hcy and CRP levels in patients with vascular dementia

Yan Ma[1], Wenping Sun[2*]

[1] Department of Neurology, Affiliated Hospital of Beihua University, Jilin, 132011, China
[2] Department of General Practice, Shanghai Songjiang District Central Hospital, Shanghai, 201600, China

[*]**Correspondence to:** sunwenping730531@126.com

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Abstract: This experiment was aimed to investigate the effect of Dengzhan Shengmai capsule combined with butylphthalide soft capsule on oxidative stress indexes and serum homocysteine (Hcy) and C-reactive protein (CRP) levels in patients with vascular dementia (VD). From July 2017 to July 2019, 123 patients with VD in our hospital were selected as the research object, and each patient was assigned a random number according to the order of treatment. Among them, No. 1 to 41 were the control group A, No. 42 to 82 were the control group B, and No. 83 to 123 were the research group. Control group A was given butylphthalide soft capsules, control group B was Dengzhanshengmai capsules, and the research group was given Dengzhanshengmai capsules combined with butylphthalide softgels. Comparison of clinical efficacy, the incidence of adverse reactions, and improvement of symptoms [Montreal Cognitive Assessment Scale (MocA) score, Vascular Dementia TCM Syndrome Differentiation Scale (SDSVD) score], vascular endothelial function [NO, endothelin 1 (ET-1)], oxidative stress [lipid peroxide (LPO), superoxide dismutase (SOD), C Dialdehyde (MDA)], endoplasmic reticulum stress response (Hcy, CRP) related indicators before and after treatment in three groups. Results showed that the total effective rate of treatment in the study group was higher than that in the control groups A and B, the difference was statistically significant (p<0.05). In symptom improvement, the MoCA score of the study group was higher than that of the control groups A and B after the treatment course, and the SDSVD score was lower than that of the control groups A and B (p<0.05); In the vascular endothelial function section, after the course of treatment, the serum NO level in the study group was higher than that in the control groups A and B, and the ET-1 level was lower than that in the control groups A and B (p<0.05). In oxidative stress experiment, after the course of treatment in the study group, the serum LPO and MDA levels were lower than those in the control groups A and B, and the SOD levels were higher than those in the control groups A and B (p<0.05). Endoplasmic reticulum stress response results showed that after the course of treatment in the study group, the serum Hcy and CRP levels were lower than those in the control groups A and B (p<0.05). In adverse reactions section, there was no significant difference in the incidence of adverse reactions among the three groups (p>0.05). Dengzhan Shengmai Capsule combined with butylphthalide soft capsule is the first treatment for VD, with definite curative effect, which can effectively reduce the damage of vascular endothelial function and inhibit oxidative stress response, antagonize the endoplasmic reticulum stress response, thereby further alleviating dementia symptoms and improving cognitive function.

Key words: Dengzhan Shengmai capsules; Butylphthalide soft capsules; Vascular dementia; Oxidative stress; Endoplasmic reticulum stress response; Vascular endothelial function.

Introduction

Vascular dementia (VD) is an acquired intelligent impairment syndrome, which is mostly caused by ischemic stroke and hemorrhagic stroke, resulting in low perfusion of memory, cognition and behavior in brain regions (1,2). According to relevant statistics, the incidence of dementia after cerebral infarction is as high as 35.80%, and there is an obvious rising trend with the aging trend of China's population (3,4). Most studies have confirmed that damage to the cholinergic system, excessive release of excitatory amino acids, calcium ion overload, neuronal apoptosis, increased content of oxygen free radicals, and inflammatory reactions are the main causes of VD (5,6). Western medicine takes antiplatelet, antihypertensive, blood glucose and lipid regulation as the main treatment strategies, but the overall effect is not ideal due to the complicated pathogenesis of VD. In recent years, traditional Chinese medicine (TCM) has made up for the deficiency and limitation of western medicine treatments on VD through holistic, comprehensive and dynamic methods. According to traditional Chinese medicine, VD belongs to the categories of "amnesia", "depression syndrome" and "dementia". The deficiency of spleen and kidney is the cause of the disease, and phlegm stasis is the standard of the disease (7,8). Dengzhan Shengmai capsule is Chinese medicine, which has the functions of activating blood and removing blood stasis and activating collaterals. However, the therapeutic effect of combined application of Dengzhan Shengmai Capsule and butylphthalide soft capsule on VD patients still needs to be confirmed by relevant data. Based on this, the breviscapine shengmai capsule combined with butylphthalide soft capsule was used for the first time in this study to investigate its effect on oxidative stress index and ER stress response of VD patients.

Materials and Methods

General information

A total of 123 VD patients in our hospital from July 2017 to July 2019 were enrolled as the research subjects. A random number was assigned to each patient according to the order of visit, and those with No. 1-41 were control group A, those with No. 42-82 were control group B, and those with No. 83-123 were research group. There was no significant difference in basic data of the three groups such as age, disease course, sex, body mass index (BMI), complications, degree of illness ($P > 0.05$), as shown in Table 1. This study was approved by the medical ethics committee of our hospital.

In this study, the steps of each section of materials and methods are shown alphabetically so that the steps of each section are well separated and understandable.

Criteria

Inclusion criteria

(A) those were confirmed by imaging examinations such as head CT or magnetic resonance imaging (B) those were accompanied by the clinical manifestations such as memory loss, intellectual loss, emotional control, and social behavior function loss due to the impairment of daily life; (C)Those having a score of Mini-Mental State Examination (MMSE) (9). within 12-24 points (D). Those have main syndromes of mental decline, slow response, dizziness, tinnitus and indolence according to traditional Chinese medicine (E) those with a history of stroke; (F) the clinical data were complete, and the patients and their families signed the informed consent.

Exclusion criteria

(A) patients are allergic to Dengzhan Shengmai Capsule and butylphthalide soft capsule;(B) Patients with mixed dementia, patients with brain trauma or dementia caused by other factors; (C) patients with severe gastrointestinal diseases;(D) patients with organic lesions of the liver, kidney and other important organs;(E) patients with cardiogenic cerebral embolism or diseases of the blood system;(F) those with severe aphasia or speech disorder;(G) those with abnormal mental behavior.

Elimination criteria, (A) self-withdrawing patient; (B) those show serious adverse reactions or complications and need to terminate treatment or change the plan; (C) Patients excluded by the researchers because of poor compliance. After eliminating the cases, the cases were re-included according to the inclusion criteria, and the cases were guaranteed to be 1:1 in number. The number of eliminated cases should be less than 5.0% of the total number of cases.

Method

Treatment method

After admission, all three groups were given basic treatment such as anti-platelet aggregation, improvement of microcirculation, and brain metabolic agents. On this basis, the control group A was orally administrated with butylphthalide soft capsule (CSPC NBP Pharmaceutical Co., Ltd., SFDA approval number H20050299), with a dose of 200 mg per each time, 3 times a day. Control group B was orally administrated with Dengzhan Shengmai Capsule (Yunnan Biovalley Pharmaceutical Co., Ltd., SFDA approval number Z20026439), with a dose of 0.36g per each time, 3 times a day. The research group was applied with Shengmai Capsule combined with butylphthalide soft capsule with similar dose and frequency as groups A and B. All three groups received continuous treatment for 3 months.

Detection method

In the fasting state, 9 mL of venous blood was collected, centrifuged for 12 min at a rate of 3000 r/min to extract serum and stored it at -20℃. (A) serum levels of nitric oxide (NO), endothelin 1 (et-1) and superoxide dismutase (SOD) were detected by enzyme-linked immunosorbent assay (ELISA) using the kit purchased from Shanghai Zeye Biotechnology Co., Ltd. (B) serum lipid peroxides (LPO) level was detected by thiobarbital acidification method, and serum malondialdehyde (MDA) level was detected by thiobarbital chromogenic method. The kit was purchased from Shanghai Xitang Biotechnology Co., Ltd. (C) serum c-reactive protein (CRP) level was detected by immunoturbidimetry using the kit purchased from Getein Biotech Co., Ltd. (D) serum homocysteine (Hcy) level was detected by fluorescence polarization immunoassay using the kit purchased from Shanghai Huding Biotechnology Co., Ltd. The above operations were carried out in strict accordance with the kit instructions.

Table 1. Comparison of general information of the three groups.

Normal information	Research group (n=41)	Control group A (n=41)	Control group B (n=41)	F/χ^2	P
Gender (male/female)	25/16	27/14	29/12	0.868	0.648
Age (years)	54~75(63.85±4.36)	53~78(64.75±3.50)	52~79(64.28±3.94)	0.533	0.588
BMI (kg/m^2)	17.6~26.3(21.79±2.07)	17.4~26.5(20.86±1.45)	17.2~26.7(21.33±1.83)	2.732	0.069
Course of disease (years)	0.6~3.9(2.63±0.52)	0.8~4.2(2.59±0.47)	0.5~4.1(2.70±0.61)	0.442	0.644
Mild	19(46.34)	17(41.46)	21(51.22)	0.785	0.676
Moderate	22(53.66)	24(58.54)	20(48.78)		
Peripheral vascular disease	4(9.76)	5(12.20)	3(7.32)	2.260	0.972
Chronic obstructive pulmonary disease	6(14.63)	4(9.76)	5(12.20)		
Diabetes	3(7.32)	4(9.76)	2(4.88)		
Hypertension	15(36.59)	17(41.46)	19(46.34)		
Hyperlipidemia	10(24.39)	8(19.51)	9(21.95)		

Efficacy criteria

MMSE score was used to evaluate the efficacy of the three groups: after treatment, the increase of MMSE score ≥5 was marked as significantly effective; After the treatment, the 5> MMSE score increase ≥2 was marked as effective; After treatment, if it does not reach the significantly effective or effective, it is marked as ineffective. Overall treatment effect = significant effective + effective.

Observation indicators

(A) clinical efficacy. (B) Montreal Cognitive Assessment Scale (MocA) (10). and vascular dementia syndrome differentiation Scale (SDSVD) (11). were used to evaluate and compare the improvement of cognition and dementia symptoms before and after treatment in the three groups, among which MocA score totaled 30 points, which was positively correlated with Cognitive function; SDSVD score was assessed from aspects of memory, pain, claw nail, complexion, color quality, pulse, etc., with a total of 30 points, and the score was negatively correlated with the improvement of dementia symptoms. (C) vascular endothelial function (serum NO, ET-1) was compared between the three groups before and after treatment. (D) the three groups of oxidative stress (serum LPO, MDA, SOD) were compared before and after treatment. (E) ER stress response (serum Hcy, CRP) was compared between the three groups before and after treatment. (F) the incidence of adverse reactions (nausea, vomiting, elevated transaminase, dizziness) in the three groups was compared.

Statistical method

SPSS 22.0 software was used to analyze and process data. The measurement data were expressed as ($\bar{x}$ ±s), the *t*-test and the one-way analysis of variance were used for the comparison between groups, and the LSD t-test was used for the multiple comparisons. The count data were expressed by n (%), and χ^2 test was used for comparison between groups. The difference was considered statistically significant when $p<0.05$.

Results

Clinical efficacy

The overall effective rate of treatment in the study group was higher than that in the control group A and B, and the difference was statistically significant (p<0.05), shown in Table 2.

Symptom improvement

There was no significant difference in MoCA and SDSVD scores between the three groups before treatment (p>0.05). After treatment, the MoCA score in the study group was higher than that in the control group A and B, and the SDSVD score was lower than that in the control group A and B (p<0.05), as shown in Table 3.

Vascular endothelial function index

There was no significant difference in levels of serum NO and ET-1 between the three groups before treatment (p>0.05). After treatment, the serum NO level of the study group was higher than that of the control group A and B, and the level of ET-1 was lower than

Table 2. Comparison of clinical efficacy of 3 groups [n (%)].

Group	Number of cases	Significantly effective	Effective	Ineffective	Total efficiency
Research	41	25 (60.98)	14 (34.15)	2 (4.88)	39 (95.12)
Control A	41	17 (41.46)	15 (36.59)	9 (21.95)	32 (78.05)
Control B	41	16 (39.02)	14 (34.15)	11 (26.83)	30 (73.17)
χ^2					7.418
p					0.025

Table 3. Comparison of symptom improvement among 3 groups ($\bar{x}$ ±s, points).

Group	Number of cases	MoCA		SDSVD	
		Before treatment	After the course of treatment	Before treatment	After the course of treatment
Research group	41	18.41±2.89	24.82±2.15	18.12±2.83	9.75±1.04
Control group A	41	17.92±2.51	21.75±2.74	17.31±2.69	13.25±1.26
Control group B	41	18.76±2.95	20.47±2.94	17.98±2.76	13.79±1.32
F		0.938	29.591	1.008	134.123
P		0.394	<0.001	0.368	<0.001

Table 4. Comparison of the levels of vascular endothelial function indexes among the 3 groups ($\bar{x}$ ±s).

Group	Number of cases	NO (μmol/L)		ET-1 (μg/L)	
		Before treatment	After the course of treatment	Before treatment	After the course of treatment
Research group	41	65.41±9.84	85.27±11.41	89.24±14.32	72.31±11.25
Control group A	41	64.92±8.99	78.91±10.25	93.25±15.16	85.25±13.26
Control group B	41	66.01±10.02	77.85±9.98	88.16±13.78	86.12±13.74
F		0.132	5.916	1.416	14.980
P		0.877	0.004	0.247	<0.001

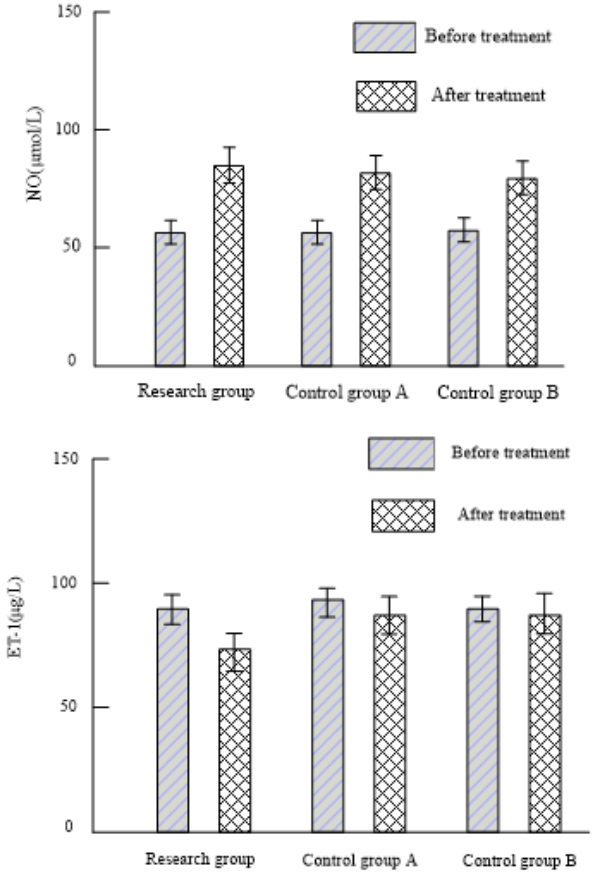

Figure 1. Comparison of serum NO and ET-1 levels in three groups before and after treatment.

that of the control group A and B ($p<0.05$), as shown in Table 4 and Figure 1.

Oxidative stress indexes

There was no significant difference in LPO, MDA and SOD before treatment in the three groups ($p>0.05$). After the treatment, serum LPO and MDA levels in the research group were lower than those in the control group A and B, and the SOD level was higher than that in the control group A and B ($p<0.05$), as shown in Table 5 and Figure 2.

Indicators of the endoplasmic reticulum stress response

There was no significant difference in serum Hcy and CRP levels between the three groups before treatment ($p>0.05$). Serum Hcy and CRP levels in the research group were lower than those in the control group A and B after treatment ($p<0.05$), as shown in Table 6 and figure 3.

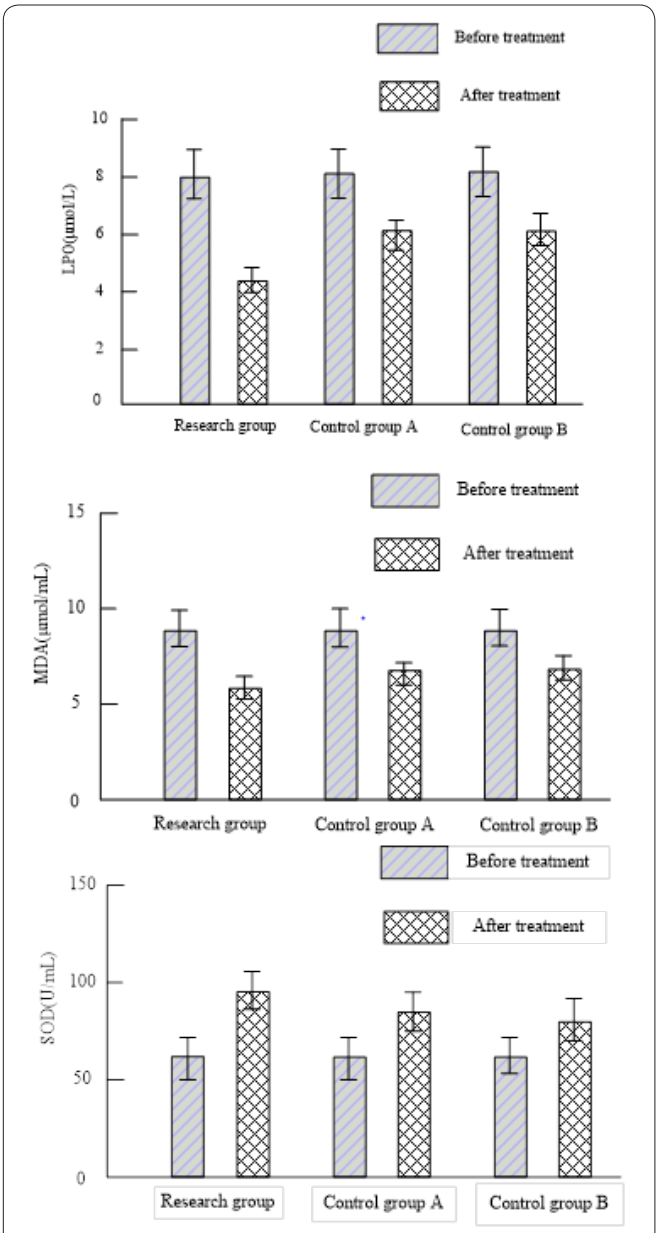

Figure 2. Comparison of serum LPO, MDA and SOD levels of three groups before and after treatment.

Incidence of adverse reactions

There was no statistically significant difference in the incidence of adverse reactions among the three groups ($p>0.05$), as shown in Table 7.

Discussion

Studies have shown that oxidative stress injury and inflammatory response play an important role in the development of VD induced by chronic cerebral hypo-

Table 5. Comparison of oxidative stress indicators of the three groups ($\bar{x}\pm s$).

Group	Number of cases	LPO(μmol/L)		MDA(μmol/ml)		SOD(U/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	41	7.89±1.30	4.37±0.86	8.97±1.65	5.32±1.67	64.51±9.89	96.85±10.56
Control group A	41	7.94±1.25	6.14±0.94	9.12±1.70	6.25±1.64	65.24±8.54	87.41±9.42
Control group B	41	7.92±1.32	6.27±0.95	9.24±1.76	6.37±1.71	64.98±8.91	85.26±9.13
F		0.016	54.866	0.258	4.835	0.067	16.485
p		0.985	<0.001	0.773	0.010	0.935	<0.001

Table 6. Comparison of three groups of indicators related to endoplasmic reticulum stress response ($\bar{x}\pm s$).

Group	Number of cases	Hcy (mmol/L)		CRP (mg/L)	
		Before treatment	After the course of treatment	Before treatment	After the course of treatment
Research	41	29.36±8.31	13.25±5.12	4.97±0.69	4.02±0.31
Control A	41	30.15±8.47	16.47±5.74	5.12±0.71	4.32±0.37
Control B	41	29.78±8.56	17.12±6.09	5.08±0.72	4.36±0.38
F		0.090	5.488	0.495	11.255
p		0.914	0.005	0.611	<0.001

Table 7. Comparison of the incidence of adverse reactions among 3 groups [n (%)].

Group	Number of cases	Feel sick and vomit	Increased transaminase	Dizziness	Total incidence
Research	41	3 (7.32)	2 (4.88)	2 (4.88)	7 (17.07)
Control A	41	3 (7.32)	2 (4.88)	0 (0.00)	5 (12.20)
Control B	41	2 (4.88)	0 (0.00)	2 (4.88)	4 (9.76)
χ^2					1.006
p					0.605

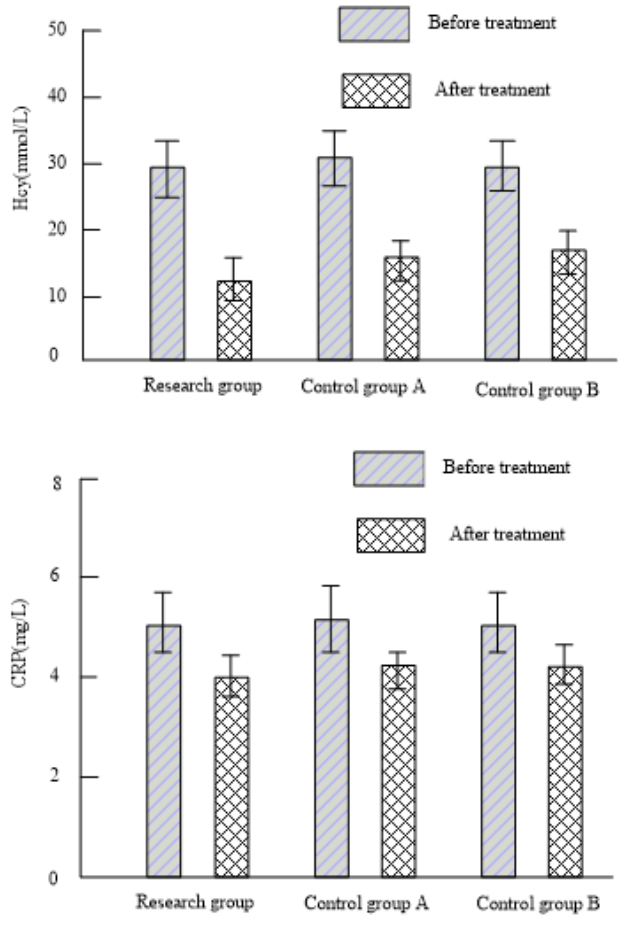

Figure 3. Comparison of serum Hcy and CRP levels in three groups before and after treatment.

perfusion (12,13). They can accelerate atherosclerosis, reduce cerebral blood perfusion, cause abnormal brain metabolism, lead to structural and functional damage of hippocampal tissue related to learning and memory, increase the risk of cognitive impairment, and eventually induce dementia (14). Therefore, the main principle of the treatment of VD is to reduce the body's inflammatory response, inhibit the oxidative stress response, and promote the recovery of brain function.

Traditional Chinese medicine holds that VD has the characteristics of asthenia in origin and asthenia in superficiality, with a mixture of asthenia and sthenia. According to *Huangdi Neijing*, "the brain is the sea of marrow, and if the medulla is insufficient, the brain will turn to tinnitus, blindness and laches." As recorded in *the correction of the errors of medical works*, "A quick memory is not from the heart but mind". Therefore, it can be seen that viscera and blood are both deficient, qi and blood cannot nourish the brain, phlegm and blood stasis are endogenous, turbidity toxin is produced as the passage of time, and the cerebral collateral is blocked, and finally the memory gradually declines, which is the main pathological mechanism of VD. Therefore, the treatment focuses on removing turbidity, promoting blood circulation and removing blood stasis (15,16). Dengzhan Shengmai capsule is mainly composed of Erigeron breviscapus, ginseng, Schisandra fruit, ophiopogonum and other traditional Chinese medicines. Erigeron breviscapus can activate blood and remove blood stasis and relieve pain; Ginseng can greatly improve the vitality, complex pulse solid, spleen and lung, calm mind; Schisandra fruit has the function of enhancing qi while nourishing fluid Yin and enriching yin and nourishing kidney; Ophiopogon japonicus has the function of clearing heat and detoxification, producing saliva and quenching thirst, eliminating phlegm and vomiting, and nourishing yin and moisturizing lung. All the drugs together can realize the function of tonifying qi and yin and invigorating the circulation of the brain. Yu Lu et al. (17) showed that adding the Dengzhan Shengmai capsule based on conventional western medicine treatment could effectively inhibit the cognitive dysfunction of VD patients. On this basis, this study confirmed that the first combination treatment of Dengzhan Shengmai capsule and butylphthalide soft capsule significantly improved the curative effect and the cognitive function of VD patients, and their dementia symptoms were significantly improved. It may be because the butylphthalide soft capsule is a synthetic racemide, which can block multiple pathological links of brain injury caused by ischemic stroke (18,19). increase blood flow in the ischemic area, regulate microcirculation in the ischemic area, antagonize nerve cell apoptosis, and repair the damaged central nervous system; and Dengzhan Shengmai capsule is

rich in flavonoids such as breviscapus ethyl, which can regulate microcirculation, reduce vascular resistance, and increase brain perfusion (20). The combination of the two plays a good synergistic role, which is conducive to strengthening the therapeutic effect, correcting cognitive and intellectual disorders, and alleviating the symptoms of VD dementia.

Vascular endothelial dysfunction leads to excessive vasoconstriction and cerebral blood perfusion insufficiency, which is one of the essential reasons for progressive cognitive impairment in VD patients (21,22). Vasoactive substances such as ET-1 and NO can indirectly reflect the function of endothelial cells. The data of this study showed that the serum ET-1 level in the study group showed a decreasing trend and the level of NO showed an increasing trend after the treatment, and the change range was greater than that in the control group A and B. It can be speculated that the combination of Dengzhan Shengmai capsule and butylphthalide soft capsule can regulate the expression of ET-1 /NO by increasing the vascular endothelium NO, affect the cerebral vasoconstriction or relaxation, ensure the nutrition supply of damaged nerve cells, and achieve the purpose of inhibiting the perfusion reconstruction in the damaged area, so as to further optimize the cognitive function. In addition, Aalling N et al (23). found that oxidative stress is also the important pathologic basis of VD, ischemia oxygen deficit can activate the oxidative stress reaction to synthesize a large number of oxygen free radicals, induce lipid peroxidation, over-expression of excessive oxidation metabolites, thus increasing antioxidant material consumption, causing the body oxidation/antioxidation disorder, changing the nerve cell membrane permeability, aggravating neurologic injury (24,25). LPO, MDA and SOD are the indicators of oxidative stress that have been widely studied. Among them, LPO and MDA are oxidative metabolites whose overexpression can activate oxidative stress and cause brain dysfunction. SOD is an antioxidant index, which can inhibit the generation of oxygen free radicals and reduce oxidative stress damage. In this study, it was found that the combined application of Dengzhan Shengmai capsule and butylphthalide soft capsule could exert the effect of quininic acid in ercoffeine, enhance the activity of SOD, remove excessive oxygen free radicals, antagonize lipid peroxidation, balance the anti-oxidation mechanism in the brain, and thus alleviate the damage of oxygen free radicals to brain tissue. It can be speculated that regulating the levels of LPO, MDA and SOD by taking Dengzhan Shengmai capsule combined with butylphthalide soft capsule might be one of the mechanisms to reduce the severity of VD patients.

Niu Xiaoli (26). established a VD mouse model and found that ER stress plays an important role in the development of VD, which can improve the learning and memory ability of VD rats by inhibiting the apoptosis of hippocampal neurons. In addition, ER stress activation can promote the formation of complexes of TNF receptor-related factor-2 and apoptotic signal-regulated kinase-1 through the IRE-1α pathway, activate nuclear transcription factors, participate in the transcriptional regulation of inflammatory genes, and mediate the release of a large number of inflammatory cytokines such as Hcy and CRP together with the JNK signaling pathway, aggravating macrophage infiltration and thus exerting a certain effect on cell vitality and cell recovery (27, 28). Through the analysis of ER stress response before and after treatment, it was found that the serum levels of Hcy and CRP in the three groups after treatment were lower than those before treatment, suggesting that either single-use of Dengzhan Shengmai capsule or butylphthalide soft capsule or combined use of the two can inhibit ER stress response in VD patients. Further comparison of the difference in ER stress response after treatment in the three groups showed that after the treatment, serum Hcy and CRP levels in the research group were significantly lower than those in the control group A and B. These results suggest that Dengzhan Shengmai capsule combined with butylphthalide soft capsule can reduce endoplasmic reticulum stress response, antagonize inflammation-related signaling pathways, prevent apoptosis of hippocampal neurons, and alleviate ischemic injury of neurons through the efficacy of celery seeds and apigenin. It was speculated that regulating the er stress response by jointly taking Dengzhan Shengmai capsule and butylphthalide soft capsule may be an important mechanism to improve the cognitive function of VD patients. However, in the early stage of VD, whether Dengzhan Shengmai capsule combined with butylphthalide soft capsule can regulate serum Hcy and CRP levels, so as to achieve the ultimate goal of changing the level of er stress unfolded protein in cerebrovascular epithelial cells and protecting the body still needs further in-depth consideration. This study also found that the combined application of Dengzhan Shengmai capsule and butylphthalide soft capsule did not increase the incidence of adverse reactions, showing high safety.

Recently, investigation of genomic instabilities in these populations who are susceptible to dementia has been interested (29). The use of new technologies such as genome editing will be very useful in this research (30).

In conclusion, the combined application of Dengzhan Shengmai capsule and butylphthalide soft capsule as a treatment for the first time has a definite effect on VD, which can effectively reduce vascular endothelial function damage, inhibit oxidative stress response, and antagonize endoplasmic reticulum stress response, so as to further alleviate the symptoms of dementia and improve cognitive function.

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References

1. Yang J, Yao Y, Wang L, Yang C, Wang F, Guo J, Wang Z, Yang Z, Ming D. Gastrin-releasing peptide facilitates glutamatergic transmission in the hippocampus and effectively prevents vascular dementia induced cognitive and synaptic plasticity deficits. Exp Neurol 2017; 287:75-83.

2. Schmitz M, Hermann P, Oikonomou P, Stoeck K, Ebert E, Poliakova T, Schmidt C, Llorens F, Zafar S, Zerr I. Cytokine profiles and the role of cellular prion protein in patients with vascular dementia and vascular encephalopathy. Neurobiol Aging 2015; 36(9):2597-606.

3. Meijun L, Xiaodong Zh, Jin H. Effect of rehabilitation training on P300 and cognitive function in patients with vascular dementia. Chin J Phys Med Rehabil 2019; 41(9):679-681.
4. Yueying Ch, Xiaonan S, Shulong Y. The role of inflammatory factors in the pathogenesis of vascular dementia. Chin J Biochem Mol Biol 2019; 35(07):693-699.
5. Liu TH, Tsai TY. Effects of equol on deoxycorticosterone acetate salt-induced hypertension and associated vascular dementia in rats[J]. Food Funct 2016; 7(8):3444-3457.
6. Hsu PF, Pan WH, Yip BS, Chen RC, Cheng HM, Chuang SY. C-reactive protein predicts incidence of dementia in an elderly Asian community cohort. J Am Med Dir Assoc 2017; 18(3):277-e7.
7. Liang Xiaona, Lin Juan, Li Xin et al. Effect of compound Danshen tablets and its prescription on the improvement of learning and memory ability in vascular dementia model rats and the mechanism of action. Chin Tradit Herb Drugs 2019; 50(12):2884-2890.
8. Sheng Xue. A study on the law of traditional Chinese medicine clinical medication on vascular dementia based on association rules. J Shandong University Tradit Chin Med 2018; 1-68.
9. Dinomais M, Celle S, Duval GT, Roche F, Henni S, Bartha R, Beauchet O, Annweiler C. Anatomic correlation of the mini-mental state examination: a voxel-based morphometric study in older adults. PLoS One 2016; 11(10).
10. Angermann S, Baumann M, Steubl D, Lorenz G, Hauser C, Suttmann Y, Reichelt AL, Satanovskij R, Sonntag F, Heemann U, Grimmer T. Cognitive impairment in hemodialysis patients: Implementation of cut-off values for the Montreal Cognitive Assessment (MoCA)-test for feasible screening. PloS One 2017; 12(10).
11. Ranran Y. Systematic evaluation and Meta analysis of acupuncture therapy for vascular dementia. J Shandong University Tradit Chin Med 2018; 1-52.
12. Staszewski J, Skrobowska E, Piusińska-Macoch R, Brodacki B, Stępień A. IL-1α and IL-6 predict vascular events or death in patients with cerebral small vessel disease—Data from the SHEF-CSVD study. Adv Med Sci 2019; 64(2):258-66.
13. Liu Haifeng, Sun Huanhuan. Effect of probucol combined with rosuvastatin on oxidative stress response and apolipoprotein expression in patients with vascular dementia. Chin J Pract Med 2019; 46(2):116-118.
14. Liu QQ, Zhong D, Zhang X, Li GZ. IL-10 targets Th1/Th2 balance in vascular dementia. Eur Rev Med Pharmacol Sci 2018; 22(17):5614-9.
15. Shanshan L. Clinical observation on the treatment of vascular dementia by tonifying kidney, activating blood and removing phlegm. J Shandong University Tradit Chin Med 2018; 1-47.
16. Ly Jingmin. Evidence evaluation and evidence-based practice of traditional Chinese medicine in the treatment of vascular dementia. J Guangzhou University Tradit Chin Med 2017; 1-49.
17. Yu Lu, Aynur, Du Zehui et al. Efficacy and mechanism of Dengzhan Shengmai capsule in patients with vascular cognitive dysfunction. World Chin Med 2019; 14(8):2109-2112.
18. Lifeng L, Aiqin Q, Xiuqin L. Effect of Wenpi Tongluo Kaiqiao decoction combined with butylphthalide on Vascular dementia in the elderly and on plasma homocysteine and inflammatory factors. Chin Arch Tradit Chin Med 2018; 36(5):1262-1265.
19. Tao F, Xiaopeng Y. Effects of butylphthalide on the expression of iNOS and MG in hippocampus of rats with chronic cerebral ischemia. Chin J Pract Nervous Dis 2018; 21(11):1171-1176.
20. de Montgolfier O, Pinçon A, Pouliot P, Gillis MA, Bishop J, Sled JG, Villeneuve L, Ferland G, Lévy BI, Lesage F, Thorin-Trescases N. High systolic blood pressure induces cerebral microvascular endothelial dysfunction, neurovascular unit damage, and cognitive decline in mice. Hypertens 2019; 73(1):217-28.
21. Singh P, Gupta S, Sharma B. Antagonism of endothelin (ETA and ETB) receptors during renovascular hypertension-induced vascular dementia improves cognition. Curr Neurovasc Res 2016; 13(3):219-29.
22. Wang Yini, Wu Liying. Effect of folic acid combined with vitamin B12 on plasma Hcy and inflammatory factors levels and vascular wall endothelial function in vascular dementia patients with type H hypertension. Int Med Health Guid News 2018; 24(6):888-891.
23. Aalling N, Hageman I, Miskowiak K, Orlowski D, Wegener G, Wortwein G. Erythropoietin prevents the effect of chronic restraint stress on the number of hippocampal CA3c dendritic terminals—relation to expression of genes involved in synaptic plasticity, angiogenesis, inflammation, and oxidative stress in male rats. J Neurosci Res 2018; 96(1):103-16.
24. Li X, Lu F, Li W, Qin L, Yao Y, Ge X, Yu Q, Liang X, Zhao D, Li X, Zhang J. Edaravone injection reverses learning and memory deficits in a rat model of vascular dementia. Acta Biochim Biophys Sin 2017; 49(1):83-9.
25. Ravindran S, Swaminathan K, Ramesh A, Kurian GA. Nicorandil attenuates neuronal mitochondrial dysfunction and oxidative stress associated with murine model of vascular calcification. Acta Neurobiol Exp 2017; 77:57-67.
26. Xiaoli N. Effects of butylphthalide on cognitive function and expression of Shh/Ptch1 signaling pathway and endoplasmic reticulum stress-related proteins in rats with vascular dementia. J Hebei Med University 2019.
27. Camargo LL, Harvey AP, Rios FJ, Tsiropoulou S, Da Silva RD, Cao Z, Graham D, McMaster C, Burchmore RJ, Hartley RC, Bulleid N. Vascular Nox (NADPH oxidase) compartmentalization, protein hyperoxidation, and endoplasmic reticulum stress response in hypertension. Hypertens 2018; 72(1):235-46.
28. Hong G, Li H, Chunguang X. Experimental study on early application of blood activating components in Shengi Compound Recipe to regulate endoplasmic reticulum stress-related genes in diabetic macrovascular lesions in KKAy mice. Lishizhen Med Mater Med Res 2019; 30(07):1547-1551.
29. Biglari S, Kamali K, Banihashemi S, Faal Sezavari A, Aghajanpour-Mir SM, Behjati F. Investigation of Aneusomy of Chromosome 21 in the Micronuclei of 13 Patients with Early Onset Alzheimer's Disease Using Fluorescence in Situ Hybridization: A Pilot Study. Rep Biochem Mol Biol 2020; 8(4): 446-453.
30. Bordbar M, Darvishzadeh R, Pazhouhandeh M, Kahrizi D. An overview of genome editing methods based on endonucleases. Modern Genetics J 2020; 15(2): 75-92.