CLINICAL RESEAPCH

**The Effects of Donepezil Combined with Butylphthalide on Endothelial Function, Oxidative Stress and Cognitive Function of Patients with Vascular Dementia**

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**Keywords**

Donepezil, Vascular dementia, Endothelial function, Oxidative stress, Cognitive function

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**Abstract**

**Objective** To investigate the effect of donepezil combined with butylphthalide on endothelial function, oxidative stress and cognitive function in patients with vascular dementia (VD). **Methods** A total of 102 patients with VD admitted to our hospital from September 2017 to October 2019 were randomly divided into observation group (51 cases), which was treated with butylphthalide and control group (51 cases), which was treated with donepezil on the basis of the control group. The endothelial function, oxidative stress and cognitive function of the two groups of patients were observed before and after treatment. **Results** After treatment, the MMSE scores of the two groups were higher than those before treatment (*P*<0.05), and the observation group was greatly higher than the control group (*P*<0.05). After treatment, the levels of endothelin (ET) and nitric oxide (NO) in the two groups were significantly lower than those before treatment (*P*<0.05), and the observation group was obviously lower than the control group (*P*<0.05). After treatment, the levels of malondialdehyde (MDA) in the two groups were sharply lower than those before treatment (*P*<0.05), and the observation group was greatly lower than the control group (*P*<0.05). Moreover, compared with before treatment, the levels of superoxide dismutase (SOD) in the two groups were significantly higher than those before treatment (*P*<0.05), and the observation group was noticeably higher than the control group after treatment (*P*<0.05). **Conclusion** Donepezil combined with butylphthalide showed a high efficacy in the treatment of VD patients, and the combined therapy can improve the cognitive function, endothelial function and oxidative stress of patients with VD.

**Introduction**

The incidence of vascular dementia (VD) in China is increasing annually [1]. VD refers to the brain tissue ischemia, hypoxia, and hypoperfusion caused by cerebrovascular disease, resulting in the damage of local neurons in the brain tissue, thereby causing dementia syndrome that is mainly manifested as cognitive dysfunction. The pathogenesis of VD has not yet been clinically clarified. Most scholars believe that brain tissue oxidative stress injury and endothelial function damage play an important role in the development of VD [2]. Butylphthalide is a self-developed anti-ischemic drug in China, and has achieved certain effects on the treatment of VD. Domestic research has found that the combination of drugs can be used for multi-channelled, multi-targeted, multi-stepped treatment, with a significantly better therapeutic effect than that of the use of a single drug but without increasing adverse reactions [3]. Donepezil is a drug approved by the US Food and Drug Administration (FDA) for the treatment of Alzheimer’s disease. In recent years, some studies have applied it in the treatment of VD. Although it has achieved certain therapeutic effects, its clinical feasibility and safety still remains controversial [4]. In this regard, this study adopted the combined therapy of donepezil and butylphthalide to treat patients with VD, and observed the effects of the combined treatment on the endothelial function, oxidative stress and cognitive function of VD patients, and aimed at investigating the feasibility of donepezil combined with butylphthalide in the treatment of VD. The report is as follows.

**Materials and methods**

**General information**

A total of 102 VD patients admitted to our hospital from September 2017 to October 2019 were selected as the research subjects. Inclusion criteria: cerebrovascular disease was confirmed by magnetic resonance imaging (MRI) or cranial CT; the MMSE score was 10-20 points [5]; no other anti-dementia drugs were used in the past 3 months. Exclusion criteria: dementia caused by neurosis, delirium or Alzheimer's disease; patients with severe heart, liver, or kidney insufficiency; patients with severe neurological impairment or history of mental illness. According to the random number table method, 102 patients were divided into observation group and control group, with 51 cases in each group. In the observation group, there were 28 male and 23 female patients aged 50-75 years old, with an average age of 62.52±12.38 years old and a course of disease of 1 to 3 years (average disease course 2.13±0.78). In the control group, there were 30 male and 21 female patients aged 51-75 years old, with an average age of 63.24±12.77 years and a disease course of 1 to 3 years (average disease course 2.21±0.80years). There was no statistically significant difference between the two groups of patients in general information such as gender, age, or disease course (P>0.05), and the data were comparable. This study was reviewed by the Ethics Committee of our hospital, and all patients signed an informed consent form.

**Methods**

All the patients were treated with conventional antihypertensive, hypoglycemic, lipid-lowering and antithrombotic drugs. On the basis of conventional treatment, the patients in the control group was orally administrated with butylphthalide (Enbipu Pharmaceutical Co., Ltd., Sinopharm Group H20050299) at 0.2g/time, 3 times/day for a continuous treatment of 2 months. The patients in the observation group were orally given donepezil (Eisai Pharmaceutical Co., Ltd., National Medicine Standard H20070181) at 5 mg/time, once/day. The drug was taken at night before going to bed on the basis of the control group for 2 months of continuous treatment.

**Observation indicators**

**Cognitive function**

Before and after treatment, MMSE was used to evaluate the patient's cognitive function. The scale covers items including attention, time orientation, reading comprehension, drawing, language comprehension, language expression, short-term memory, speech expression and calculation ability, etc.. The full score of the scale was 30 points, with a higher score indicating a higher cognitive function.

**Endothelial function**

Enzyme-linked immunosorbent assay (ELISA) was performed to determine the level of endothelin (ET) before and after treatment. The kit was purchased from Shanghai Lufeng Biotechnology Co., Ltd.. Nitrate/Nitrite Colorimetric Assay Kit (Shanghai Baili Biotechnology Co., Ltd., China) was used to measure the level of nitric oxide (NO).

**Oxidative stress level**

Before and after treatment, 3mL of venous blood was taken from the patients, centrifuged to take the supernatant, and the level of malondialdehyde (MDA) was determined by the thiobarbituric acid color method. The level of superoxide dismutase (SOD) was determined by ELISA (Shanghai Lufeng Biotechnology Co., Ltd.).

**Statistical processing**

SPSS 20.0 statistical software was used for data analysis. The measurement data were represented by (¯x±s), the comparison were represented by t test, the count data were represented by (%). Data were compared by chi-square test. P<0.05 was considered as statistically significant.

**results**

**Comparison of cognitive function between the two groups before and after treatment**

There was no significant difference in the MMSE scores of the two groups before treatment (P>0.05), but the MMSE scores of the two groups were significantly higher after treatment than before treatment (P<0.05), and the observation group showed a sharply higher scores than the control group (P<0.05), see Table 1.

Table 1 Comparison of cognitive function between the two groups before and after treatment（¯x±s，points）

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Groups | Cases | Before treatment | After treatment | *t* | *P* |
| Observation group | 51 | 12.56±5.37 | 16.72±4.68 | -4.171 | 0.000 |
| Control group | 51 | 12.68±5.42 | 14.68±4.52 | -2.024 | 0.046 |
| *t* |  | -0.112 | 2.239 |  |  |
| *P* |  | 0.911 | 0.027 |  |  |

**Comparison of endothelial function between the two groups before and after treatment**

There was no significant difference in the levels of ET and NO between the two groups before treatment (P>0.05). After treatment, the levels of ET and NO in the two groups were significantly lower than before treatment (P<0.05), and the observation group was greatly lower than the control group (P<0.05), see Table 2.

Table 2 Comparison of endothelial function between the two groups before and after treatment（¯x±s）

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Groups | cases | ET（ng/L） | *t* | *P* | NO（μmol/L） | *t* | *P* |
| Before treatment | After treatment | Before treatment | After treatment |
| Observation group | 51 | 146.35±13.48 | 79.65±9.34 | 29.045 | 0.000 | 93.65±11.59 | 82.36±9.62 | 5.353 | 0.000 |
| Control group | 51 | 143.68±14.21 | 105.26±11.69 | 14.911 | 0.000 | 94.12±11.63 | 89.12±10.03 | 2.325 | 0.022 |
| *t* |  | 0.974 | -12.223 |  |  | -0.204 | -3.474 |  |  |
| *P* |  | 0.333 | 0.000 |  |  | 0.838 | 0.001 |  |  |

**Comparison of oxidative stress levels between the two groups of patients before and after treatment**

There was no significant difference in the levels of MDA and SOD between the two groups before treatment (P>0.05). After treatment, the levels of MDA in the two groups were significantly lower than before treatment (P<0.05), and the observation group was obviously lower than the control group (P<0.05). After treatment, the levels of SOD in the two groups were significantly higher than before treatment (P<0.05), and the observation group was noticeably higher than the control group (P<0.05), see Table 3.

Table 3 Comparison of oxidative stress levels between the two groups before and after treatment（¯x±s）

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Groups | Cases | MDA（μmol/mL） | *t* | *P* | SOD（U/mL） | *t* | *P* |
| Before treatment | After treatment | Before treatment | After treatment |
| Observation group | 51 | 9.86±1.72 | 5.42±1.37 | 14.420 | 0.000 | 66.34±8.54 | 98.54±10.31 | -17.177 | 0.000 |
| Control group | 51 | 9.91±1.75 | 7.21±1.63 | 8.063 | 0.000 | 66.42±8.76 | 75.27±9.66 | -4.847 | 0.000 |
| *t* |  | -0.146 | -6.004 |  |  | -0.047 | 11.762 |  |  |
| *P* |  | 0.885 | 0.000 |  |  | 0.963 | 0.000 |  |  |

**Discussion**

Brain tissue ischemia is a direct cause of VD. Long-term ischemia will lead to the decline in the patient’s memory and cognitive abilities, subsequently and gradually affect attention, calculation and comprehension ability of VD patients. Thus, improving ischemia are especially important for the treatment of VD patients [6]. At present, many drugs have been used for the treatment of VD patients, among them, butylphthalide, which is an anti-ischemic drug independently developed by China, has a significant effect on improving cerebral ischemia lesions. Studies have used butylphthalide to treat patients with VD, and found that butylphthalide greatly improves the cognitive function and self-care ability of the patients [7]. Although butylphthalide has demonstrated effective in treatment patients with VD, a number of studies have shown [3,7] that the combined therapy for managing VD is more effective than using a single medication without increasing increase adverse drug reactions. Therefore, to determine another effective drug for the combined used with butylphthalide has become the key to the treatment of VD.

Donepezil, which is the second drug approved by the FDA for the treatment of Alzheimer's disease, is a selective acetylcholinesterase inhibitor that can effectively inhibit the activity of cholinergic neuroticism and improve the cholinergic state of the brain. Studies have found that [8] cholinergic nerve function defects are one of the mechanisms leading to VD. Therefore, some scholars have applied donepezil to patients with VD. Though they have achieved certain results, there are still clinical disputes about the feasibility and effectiveness of its treatment. In this regard, this study discussed the efficacy and mechanism of the combined treatment, and provided a reliable basis for the selection of clinical treatment options. The results of this study showed that the MMSE scores of the two groups were higher after treatment than before treatment (P<0.05), and the scores in the observation group was significantly higher than the control group (P<0.05), indicating that donepezil combined with butylphthalide showed a significant effect in treating VD patients and can greatly improve VD patients’ cognitive function. Therefore, according to the results of this study, donepezil combined with butylphthalide can be used for treating patients with VD.

At present, the pathological mechanism of VD has been widely discussed, and some studies have found that endothelial function damage plays an important role in the development of VD. As a vasoactive polypeptide secreted by endothelial cells, ET is the endogenous vasoconstrictor with the strongest effect and the longest duration known so far. The study found [9] that the ET level in patients with cerebrovascular disease was significantly increased, and that the ET level was positively correlated with the size of the lesion. NO is an endothelial-dependent relaxing factor, and has various functions such as regulating neuronal excitotoxicity and inflammatory damage. Increased level of NO can damage blood vessels and aggravate the symptoms of dementia. In this study, donepezil combined with butylphthalide was used to treat VD patients, and we found that the levels of ET and NO in the two groups were significantly lower after treatment than before treatment (P<0.05), and the levels were greatly lower in the observation group than the control group (P<0.05). These results indicated that the combination of the two can significantly reduce the levels of ET and NO. It is therefore speculated that the two used in combination can achieve the purpose of treating VD by reducing the damage of vascular endothelial cells.

Most scholars believe that [2,9] oxidative stress damage to brain tissues plays an important role in the development of VD. Long-term ischemia and hypoxia in brain tissue will activate the body's arachidonic acid and xanthine oxidase system, release a large amount of oxygen free radicals, reduce the level of antioxidants such as vitamin C and SOD, and increase the level of oxidation products such as MDA, thereby causing damage to neurons and eventually further aggravating the oxidative stress damage to the brain tissues. This study found that after treatment with donepezil combined with butylphthalide, in VD patients, the level of SOD was significantly increased, and that of MDA was greatly reduced, moreover, the improvement of oxidative stress in the patients treated with the combined therapy was more significant than that of the patients treated with butylphthalide alone. The reason was that donepezil can scavenge oxygen free radicals, thereby reducing the oxidative stress response and reducing further damage to brain tissues [10]. From the perspective of the treatment mechanism, it can be seen thatdonepezil combined with butylphthalide can improve endothelial function damage and oxidative stress damage, confirming the effectiveness of the combination of the two in clinical treatment of VD.

In summary, donepezil combined with butylphthalide can significantly improve the cognitive function of patients with VD, enhance patients’ endothelial function, and reduce the level of oxidative stress, therefore can be used as an effective method for the treatment of VD.

**Declaration of conflict-of-interest**

The authors declare no conflict-of –interest.

**References**

[1] WANG H,LIU N,ZHANG S,et al.Clinical Experience in Treatment of Alzheimer's Disease with Jiannao Yizhi Formula and Routine Western Medicine[J].Chin J Integr Med,2020,26(03):212-218.

[2] Wang W,Zhang Y,Yu W,et al.Bushenhuoxue improves cognitive function and activates brain-derived neurotrophic factor-mediated signaling in a rat model of vascular dementia[J]. J Tradit Chin Med,2020,40(01):49-58.

[3] Ning W,Xiao L,Ren L,et al.Possible mechanisms of lycopene amelioration of learning and memory impairment in rats with vascular dementia[J].NEURAL REGEN RES,2020,15(02):332-341.

[4] YANG Y,LIU J,FANG J,et al.Effect and Safety of Huannao Yicong Formula in Patients with Mild-to-Moderate Alzheimer's Disease: A Randomized, Double-Blinded, Donepezil-Controlled Trial[J].Chin J Integr Med,2019,25(08):574-581.

[5] Ting T,Wan X,Zheng L,et al.A donepezil/cyclodextrin complexation orodispersible film: Effect of cyclodextrin on taste-masking based on dynamic process and in vivo drug absorption[J].Asian J Pharm,2019,14(02):183-192.

[6] Xu Y,Wang X,Xu T,et al.Kai Xin San ameliorates scopolamine-induced cognitive dysfunction[J].NEURAL REGEN RES,2019,14(05):794-804.

[7] Jin B,Liu H.Comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment: systematic review and Bayesian network meta-analysis[J].NEURAL REGEN RES,2019,14(05):805-816.

[8] Chen Y,Xiao W,Li W,et al.Microbleeds in fronto-subcortical circuits are predictive of dementia conversion in patients with vascular cognitive impairment but no dementia[J].NEURAL REGEN RES,2018,13(11):1913-1918.

[9] Zhang X,Li L,Jiang T,et al.Effects of repetitive transcranial magnetic stimulation on cognitive function and cholinergic activity in the rat hippocampus after vascular dementia[J].NEURAL REGEN RES,2018,13(08):1384-1389.

[10] WANG H,ZHANG M,ZHAO J,et al.Puerarin Up-regulates Methyl-CpG Binding Protein 2 Phosphorylation in Hippocampus of Vascular Dementia Rats[J].Chin J Integr Med,2018,24(05):372-377.