

Original Research Article

Effect of butylphthalide in patients with vascular cognitive impairment

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Abstract

Purpose: To study the effects of butylphthalide in patients with vascular cognitive impairment.

Method: Sixty patients with vascular cognitive impairment were randomly divided into control group and butylphthalide (NBP) group (n = 30). Control group received blood pressure control, blood sugar control, and lipid-lowering therapies, while NBP group received butylphthalide capsules (200 mg, thrice daily). Treatments in both groups lasted for 14 days. Thereafter, Hasegawa Dementia Scale (HDS), Mini-Mental State Examination (MMSE), Activities of Daily Living Scale (ADL), and event-related potential (P300) were used to evaluate the effects of butylphthalide treatment.

Result: Following 14 days of treatment, HDS, MMSE and ADL scores of NBP group were significantly higher than those of the control group (p < 0.05). The P300 latency of NBP group was shorter than that of control group, while P300 amplitude was higher than that of control group (p < 0.05).

Conclusion: Butylphthalide treatment achieves higher scores of HDS, MMSE and ADL scores, but shorter P300 latency. These results provided good evidence of the effectiveness of butylphthalide therapy in the management of vascular cognitive impairment. However, further clinical trials are recommended prior to application in clinical practice.

Keywords: butylphthalide (NBP), Vascular cognitive dysfunction, Hasegawa Dementia Scale (HDS), Activities of Daily Living Scale (ADL), event-related potential (P300)

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INTRODUCTION

Vascular cognitive dysfunction refers to memory loss due to vascular factors, and cognitive dysfunction and an altered mental status are common clinical manifestations [1-3]. Epidemiological surveys have shown that the incidence of vascular cognitive dysfunction is approximately 1.1 - 3 % in China. The disease may gradually worsen without intervention,

leading to severe economic and medical burdens on society and families [4,5]. The incidence of vascular dysfunction is higher in males than in females. Most patients have hypertension and central nervous system localization signs. Vascular cognitive dysfunction is second only to Alzheimer's disease as a leading cause of senile dementia [6].

The incidence of vascular cognitive dysfunction is on the increase. A study showed that patients with vascular cognitive dysfunction are prone to developing dementia. Unfortunately, to date, there is still a lack of effective treatment specifically for vascular cognitive dysfunction.

DL-3-n-butylphthalide (NBP) is a synthetic chiral compound that was initially isolated from the seeds of *Apium graveolens*. Several studies have demonstrated that NBP reduces ischaemic cerebral injury by inhibiting platelet aggregation, protecting mitochondria, alleviating oxidative damage, improving microcirculation and so on [8-13]. NBP was recognized in the year 2000 by the State Food and Drug Administration of China (SFDA) as a therapeutic drug for the treatment of ischaemic stroke with good safety and tolerability [14,15].

In vitro, NBP has been shown to increase the expression of NR2B and synaptophysin in the hippocampus of aged rats and then increase in brain acetylcholine levels, which are beneficial for learning and memory [16]. Similar phenomena were observed in other studies [17]. Hence, the hypothesis was proposed that NBP may have therapeutic efficacy for patients with vascular cognitive dysfunction.

This study seeks to identify the changes in Hasegawa Dementia Scale (HDS), Mini-Mental State Examination (MMSE), and Activities of Daily Living Scale (ADL) scores and event-related potentials (P300) in patients before and after the use of butylphthalide, and to determine the effects of butylphthalide treatment on vascular cognitive dysfunction.

METHODS

A total of 60 patients with vascular cognitive dysfunction who were admitted to the Department of Neurology, Chongqing Hospital of Traditional Chinese Medicine from March 2014 to May 2017 were enrolled in this study. Each patient required brain computed tomography (CT) or magnetic resonance imaging (MRI) examination to confirm cerebral infarction.

Patients with mild to moderate vascular cognitive dysfunction according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders (4th Edn) were included in the study, while those with cognitive dysfunction and mental disorders caused by other organic diseases were excluded. All participants provided written informed consent. An independent data and safety monitoring board was responsible for monitoring the conduct and safety of the trial. This study was approved by the Ethics

Committee of the Chongqing Hospital of Traditional Chinese Medicine (no. 14-CHTC-031). Signed written informed consents were obtained from the patients and/or guardians. The study was conducted in line with the Declaration of Helsinki [18].

The 60 patients were randomly divided into an NBP group and a control group, with 30 patients in each group. The clinical features of the patients were as follows: The course of illness was 6 to 32 months, with a mean of 20.9 ± 9.7 months. The age ranged from 53 to 75 years, with an average of 64.5 ± 6.7 years. Among all the patients, 25 had a history of hypertension, 22 had a history of coronary heart disease, 26 had a history of diabetes, and 25 had a history of hyperlipidaemia. There was no significant difference between the two groups of patients in terms of sex, age, disease course, education level, or the degree of cognitive dysfunction.

Treatments

After admission, patients in both groups were given conventional basic treatment which included blood pressure control, blood sugar control, and lipid-lowering therapies, as well as treatment for myocardial ischaemia. The treatment group was also given butylphthalide soft capsules (NBP, CSPC). Bipu Pharmaceutical Co. Ltd) 200 mg, 3 times daily for 14 days.

Evaluation of treatment parameters/indices

The Hasegawa Dementia Scale (HDS), Mini-Mental State Examination (MMSE), and Activities of Daily Living Scale (ADL) and the measurement of event-related potentials (P300) were performed before and after administering butylphthalide. The effects of butylphthalide treatment on vascular cognitive dysfunction were also observed. Physical examinations, measurements of vital signs, and laboratory tests (blood chemistry panel, urinalysis, and stool analysis) were performed to determine the safety of butylphthalide. Efficacy and safety were assessed at baseline and at week 2. All interviewers and experts received uniform training on the standard administration of assessment tools and diagnosis.

Statistical analysis

All data are expressed as mean \pm SEM. Differences between multiple groups were analysed using Statistical Product and Service Solutions (SPSS) 21.0 software package (IBM, Armonk, NY, USA). Independent sample t-test

was used for comparison between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

Changes in HDS and MMSE scores before and after treatment

As shown in Table 1, the scores for butylphthalide and control groups were higher than those recorded prior to treatment ($p < 0.05$).

Changes in ADL scores and P300

The ADL scores of butylphthalide and control groups were higher than before treatment, and the butylphthalide group was better than the control group. The incubation period of P300 in butylphthalide and control groups were shortened, the amplitude increased, but the butylphthalide group but better than control group. The difference was statistically significant, as shown in Table 2.

DISCUSSION

The annual incidence of vascular dementia worldwide is approximately 5 – 9 per 1000, and its prevalence is approximately 1.1 to 3 % in China [4]. The main cause of vascular cognitive dysfunction is ischaemic cerebrovascular disease. Due to reduced blood supply to the brain tissue, cerebral perfusion is reduced, and a series of pathophysiological changes occur, such as oxidative stress and mitochondrial dysfunction. Early intervention for vascular cognitive dysfunction effectively slows the progression of cognitive impairment and even reverses cognitive impairment.

P300 amplitude determines the ability to perceive information and then determine attention, and it can also reflect a certain emotional investment [7]. The P300 latency of patients with vascular cognitive dysfunction is prolonged, and the amplitude of the wave is significantly reduced, indicating that the patient's interest in external things is reduced, and their attention is susceptible to external interference.

NBP is a nationally approved first-class drug independently researched and developed by in and by China. Its main ingredient is butylphthalide, which is derived from the seeds of *Apium graveolens* in southern China. Its mechanisms of action include the inhibition of platelet aggregation, reduction in oxidative stress damage, protection of the blood–brain barrier, protection of mitochondrial function, increase in cerebral blood flow in the ischaemic area, and the rebuilding of microcirculation in the ischaemic area [8-13]. Subsequent clinical trials further confirmed that butylphthalide has a good therapeutic effect on the ischaemic cerebrovasculature, is safe and effective, and is well tolerated [14-16].

Animal studies have found that butylphthalide increases not only the expressions of the NMDA receptor NR2B subunit and synaptic vesicle proteins in elderly rats with chronic cerebral hypoperfusion but also the levels of acetylcholine [17]. In a mouse study, butylphthalide reduced learning and memory impairment [18]. Previous studies have found that as patients recovered from stroke, even with a placebo, their cognitive impairment improved [19]. Therefore, when the initial screening of patients was performed in this study, patients with new-onset strokes and strokes within the last 3 months were selected.

Table 1: Comparison of HDS and MMSE scores of patients before treatment and 14 days after treatment

Group	n	HDS		MMSE	
		Before treatment	14 days after	Before treatment	14 days after
NBP	35	15.1±2.60	21.6±2.31*	14.4±2.41	23.4±2.37*
Control	25	14.4±1.78	17.4±2.17#	13.7±1.7	17.2±1.75#

NBP group compared with before treatment, * $p < 0.05$; compared with control group, # $p < 0.05$

Table 2: Comparison of ADL scores and P300 of patients before treatment and 14 days post-treatment

Group	n	ADL		Incubation period		P300 amplitude	
		Before	14 days after	Before	14 days after	Before treatment	14 days after
NBP	35	34.7±2.21	65.9±3.31*	349.5±17.31	295.6±14.74*	6.8±2.66	12.4±2.41*
Control	25	34.4±2.67	43.6±2.17#	381.8±12.86	381.5±11.13#	5.4±2.07	9.1±1.07#

NBP group compared with before treatment; * $p < 0.05$; compared with control group, # $p < 0.05$

All patients with known dysfunction were excluded to ensure that the results of this study were due to the therapeutic effect of butylphthalide rather than the natural recovery of acute stroke. This study demonstrated that the butylphthalide group exhibited increases in Hasegawa Dementia Scale, Mini-Mental State Examination, and activities of Daily Living Scale scores, and shortened latencies of event-related potentials, with a range of fluctuations compared with the control group. The increases were significant, which is consistent with the research of other scholars. This lends credence to the belief that the early use of butylphthalide in patients with vascular cognitive dysfunction may improve the survival rate of these patients. Previous animal experiments have found that butylphthalide improved cognitive dysfunction after ischaemia by increasing the synthesis of acetylcholine, inhibiting oxidative stress and preventing the neuropathological changes that occur after ischaemia [20]. Butylphthalide can also reduce the size of an infarct [11]. Li *et al* found that butylphthalide improved the vascular cognitive dysfunction caused by chronic cerebral hypoperfusion by regulating GDNF/GFR α 1/Ret and AKT/ERK1/2 signalling pathways [21], and they speculated that butylphthalide can improve the condition of blood vessels. The mechanisms of cognitive dysfunction may involve multiple aspects, such as oxidative stress and inflammation, which need to be further confirmed in subsequent related experiments.

Limitations of the study

The limitations of this study are that there were few participants and the observation time was short. Therefore, larger-sample studies and longer-term observations are essential to compare and analyse the therapeutic effects of butylphthalide.

CONCLUSION

Butylphthalide treatment achieves higher scores of HDS, MMSE and ADL scores, but shorter P300 latency. These results provided good evidence of the effectiveness of butylphthalide therapy in the management of vascular cognitive impairment. However, further clinical trials are recommended prior to application in clinical practice.

DECLARATIONS

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None provided.

Ethical approval

This study was approved by the Ethics Committee of the Chongqing Hospital of Traditional Chinese Medicine (no. 14-CHTC-031).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. The authors contributed equally to this research.

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