

Original Article

Efficacy of butylphthalide soft capsules in patients with vascular dementia and the relevant antioxidative mechanism

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Abstract: Background: To observe the efficacy of butylphthalide soft capsules in patients with vascular dementia. Methods: 124 patients with vascular dementia were randomly and equally divided into the research group and control group. In the control group, patients received donepezil hydrochloride tablets for 3 months, whereas those in the research group received butylphthalide soft capsules. Then the daily living activities (ADL), clinical dementia rating (CDR), mini-mental state examination (MMSE), 36-item Short-Form Health Survey (SF36), and changes in cerebral blood flow and superoxide dismutase (SOD) activity, and malonaldehyde (MDA) levels in serum in both groups were compared. Results: In the research group, a total effectiveness rate of 77.42% was significantly higher than the control group of 62.90% ($P=0.033$). After 3 months of treatment, ADL and MMSE scores in the research group were much higher than that in the control group ($P=0.000$). CDR in the research group was lower than that in the control ($P=0.000$). The SOD activity in the research group was higher than that before treatment ($P=0.000$), but not significantly different from that in the control group ($P=0.077$). The MDA levels were also decreased in both groups compared to the levels before treatment ($P=0.000$), but the decrease in the research group was more evident ($P=0.001$). Conclusion: Butylphthalide soft capsules improved the nerve function, cognitive function, and daily living activities of patients with vascular dementia, which was believed to be correlated with improvements in SOD activity and MDA levels in patients, compared with donepezil hydrochloride tablets.

Keywords: Butylphthalide soft capsules, vascular dementia, cognitive functions, superoxide dismutase activity

Introduction

Vascular dementia, a common disease in middle-aged and elderly individuals, is a type of acquired intellectual deficiency syndrome. The pathogenesis of vascular dementia correlates closely with the cerebrovascular lesions caused by small vascular disease, white matter damage, alteration in nerve transmitters, and inflammatory responses [1, 2]. Clinically, vascular disease is manifested by the gradual progressive decline or even loss of language, memory, and cognitive functions [3, 4]. In some severe cases, patients may suffer from dementia, which affects the quality of life of patients and contributes to the economic burden of the patients and their family. In recent years, the longer lifespan of the Chinese population has led to an increase in the incidence of vascular

dementia. Thus, methods to improve the cognitive function, daily living activities, and better understanding of the pathogenesis of the disease, have become a focus of current scientific research.

Butylphthalide is a multitarget drug that can mitigate cerebral ischemia and improve vascular endothelial functions. Relevant studies [5, 6] have shown that butylphthalide can protect the mitochondria and antagonize oxidative injuries. Thus, we inferred that butylphthalide could ameliorate the cognitive function of patients with vascular dementia.

In this study, we selected a total of 124 patients with vascular dementia who were admitted to the hospital for treatment between January 2016 and December 2017. Sixty-two patients

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were administered with butylphthalide soft capsules. The aim of this study was to investigate the efficacy of butylphthalide soft capsules for the treatment of vascular dementia and determine the underlying mechanism of action.

Material and methods

General data

A total of 124 patients with vascular dementia who were admitted to this hospital between January 2016 and December 2017 were enrolled in this randomized, double-blinded, and controlled study in accordance with the following inclusion and exclusion criteria.

Inclusion criteria: (1) patients conforming to the diagnostic criteria in *Diagnostic Criteria for Vascular Dementia (Draft)* as stipulated by the Neurology Society, Chinese Medical Association in 2002; (2) patients between 50 and 79 years of age, with a disease course of between 3 months and 3 years, and no relevant treatment before hospitalization; (3) patients with the manifestations of dementia within 3 months after the occurrence of cerebrovascular disease, including decline in memory and cognitive dysfunction, and a disease course longer than 3 months; (4) patients with cerebrovascular diseases in casual connection with the onset of dementia; (5) patients and their family voluntarily gave written informed consent.

Exclusion criteria: (1) patients with dementia caused by brain injury, encephalitis, or Alzheimer's disease; (2) patients with diseases of the heart, liver, or kidney; (3) patients with the malignant tumors; (4) patients with mental disorders or a history of mental disorders; (5) patients who had difficulty in cooperating with the treatment owing to severe nerve deficiency and patients who were prescribed to treat vascular dementia before hospitalization; (6) patients with blood diseases or severe ulcers in the digestive system; (7) patients with bleeding tendency; (8) patients who were allergic to or with contraindications to the drugs used in this study.

This study was approved by the Ethics Committee of the hospital. The enrolled subjects were allocated to the research group and the control group using a random digit table with 62 subjects assigned to each group.

Treatment methods

Following admission, patients in both groups were given secondary prevention of cerebrovascular disease and received the regular treatments, which included anti-platelet therapy, blood pressure control, and the regulation of blood fat. At the same time, patients were given regular rehabilitation training, based on the above treatment. The control group received 5 mg donepezil hydrochloride (Jiangsu Haosen Pharmaceutical Co., Ltd., Guoji Zhunzi H200-30472) orally, once every day. The patients in the research group received oral butylphthalide soft capsules (CSPC NBP Pharmaceutical Co., Ltd., SFDA Approval No.: H20050299), 0.2 g/time, three times per day. In both groups, the patients received medication for 3 months, consecutively.

Outcome measures

Evaluation of daily living activities: By using the scales of activity of daily living (ADL) [7], we evaluated the ADL of patients through two aspects, the instrumental activities of daily living and the physical activities of daily living. The scores ranged from 0 to 100 points, and a higher ADL score was indicative of better daily living activity.

Evaluation of cognitive function: We used the Mini-Mental State Examination (MMSE) [8] to evaluate the improvement in cognitive function for patients through the following aspects, such as orientation, attention, memory, calculation, and navigation, with a score between 0 and 30 points. A high MMSE score was suggestive of excellent cognitive function. Thereafter, the clinical dementia rating (CDR) [9] was utilized to assess the dementia status of patients. The assessment results comprised three grades: mild (1 point), moderate (2 points), and severe (3 points).

Evaluation of efficacy: All patients were scored for neurological deficits before treatment and after 3 months of treatment using the National Institutes of Health Stroke Scale (NIHSS), including speech, consciousness, hand muscle strength, walking ability, upper limb strength, the lower limb muscle strength, facial paralysis level, and gaze function, and the effect was evaluated by the degree of neurological deficit reduction. Significantly effective, scores red-

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Table 1. Comparison of the baseline data in both groups ($\bar{x} \pm s, n$)

Group	Gender (M/F)	Age (year)	Disease course (m)	MMSE (point)	ADL (point)	CDR (point)	Disease duration (year)	Concomitant diseases	Treatment history (year)
Research group	38/24	66.75±5.78	17.23±6.25	18.17±4.25	48.62±7.56	1.83±0.45	2.2±0.32	0.2±0.0.1	3±0.1
Control group	35/27	66.18±6.35	17.65±5.94	18.63±4.88	48.02±7.97	1.85±0.41	2.7±0.45	0.3±0.05	4.1±0.5
t/ χ^2	0.300*	0.523	0.354	0.560	0.430	0.259	0.312	0.212	0.425
P	0.584	0.602	0.702	0.577	0.668	0.796	0.77	0.85	0.56

Note: *for chi-square test.

used by more than 90%; excellent, for a score with a decline over 90%; effective, for a score with a decline between 46% and 89%; improved, for a score with a decline between 18% and 46%; and failure, for a score with a decline less than 18% or even an increase. The total effectiveness rate = (Excellent + Effective)/62 × 100%.

Evaluation of quality of life: To assess this parameter, the 36-item Short-Form Health Survey issued by World Health Organization [10] was applied to assess the quality of life of patients by evaluation of the following aspects: physiological function (PF), role physical (RP), vitality (VT), bodily pain (BP), general health (GH), role emotional (RE), social function (SF), and mental health (MH).

Comparison of oxidative stress markers

Prior to the treatment and after 3 months of treatment, the patients' early morning fasting elbow venous blood serum were taken, centrifuged at 3000 r/min for 15 min, and the supernatant was aspirated for detection. We detected SOD activity by using a fluorescent detection kit (Shanghai Haling Biological Technology Co., Ltd). Strictly follow the instructions of the kit, pipette 20 μ l of serum, add 75 mL $\text{Na}_2\text{CO}_3/\text{NaHCO}_2$ buffer, 20 mL 5 mM NaH_2HCL , 0.5 mL 0.3% (V/V) Triton X-100, and 0.3 mL 0.98 mM NBT 0.1 mL, mix immediately timing, 37°C, protected from light bath for 10 min, 20 mL formic acid termination reaction, E560 nM record OD value. During the same period, we also measured MDA levels by using the visible spectrophotometry and an appropriate detection kit (Shenzhen Ziker Biological Technology Co., Ltd). Strictly accordant with the instructions of the kit, draw 0.6 mL of reagent into a 1.5 mL centrifuge tube, add 0.2 mL of serum sample, mix, 90°C water bath for 30 min, the sample was

then placed in an ice bath to cool, 10000 g centrifugation at room temperature for 10 min, aspirate 1 mL of the supernatant into a glass cuvette, and measure the absorbance at 532 nm and 600 nm. The samples are recorded as A532 and A600, and the MDA content is calculated as $25.8 \times (A532-A600)$.

Alterations in brain blood flow

Transcranial doppler sonography (TCD) was used to detect the changes in blood flow of the middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), vertebral artery (VA), and basilar artery (BA) in patients in both groups before and after treatment [11].

Adverse reactions

Any increases in transaminase, emergence of nausea, discomfort in the stomach, nasal obstruction, insomnia, or rashes in patients during the treatment were deemed as adverse reactions.

Statistical analysis

The data collected in this study were computed by using SPSS 19.0 software for statistical analysis. The measurement data of intragroup before-after comparison were compared using paired *t* test and the between-group comparison was using the independent *t* test, whereas enumeration was performed using chi-square test. A *P* value of < 0.05 was considered to represent statistically significant difference.

Results

A comparison of the baseline data between two groups indicated no significant differences (*P* > 0.05; **Table 1**), suggesting that the data were comparable.

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Table 2. Comparison of the efficacy in both groups (n, %)

Group	n	Excellence	Effective	Improved	Failure	Total effectiveness rate
Research group	62	15 (24.19)	33 (53.23)	8 (12.90)	6 (9.68)	48 (77.42)
Control group	62	10 (16.13)	27 (43.55)	13 (20.97)	12 (19.35)	37 (59.68)
χ^2	-	-	-	-	-	4.526
<i>P</i>	-	-	-	-	-	0.033

Comparison of the treatment efficacy

In the research group, patients had a total effectiveness rate of 77.42%, which was significantly higher than the 62.90% observed in the control group ($P < 0.05$; **Table 2**).

Comparison of the ADL, MMSE, and CDR scores of patients before and after treatment

Three months of treatment resulted in elevation in the ADL and MMSE scores of patients in both groups, but the increase in the research group was much greater than that in the control group ($P < 0.05$). Over the treatment period, patients in both groups experienced a decrease in CDR compared to the levels before treatment, but the decrease in the research group was more obvious than that in the control group ($P < 0.05$; **Table 3** and **Figure 1**).

Comparisons of the SOD activity and MDA levels before and after treatment

The SOD activity and MDA levels in both groups prior to treatment were not significantly different ($P > 0.05$). After the treatment period, SOD activity in the research group was higher than that before treatment ($P < 0.05$), but not significantly different from that in the control group ($P > 0.05$). The MDA levels were also decreased in both groups compared to the levels before treatment ($P < 0.05$), but the decrease in the research group was more evident ($P < 0.05$; **Table 4** and **Figure 2**).

Comparison of the blood flow in the brain before and after treatment

Prior to treatment, we compared the blood flow in the MCA, ACA, PCA, VA, and BA in both groups and found no statistically significant differences ($P > 0.05$). After treatment, significant elevations in the blood flow to all arteries were observed in both groups ($P < 0.05$), with the parameters of patients in the research group

superior to those in the control group ($P < 0.05$; **Table 5** and **Figure 3**).

Comparison of the quality of life

Before treatment, the VT, BP, GH, RE, SF, MH, and total scores were not significantly different in either group ($P > 0.05$). Following treatment, VT, BP, GH, RE, SF, MH and total scores in both groups were significantly higher than the levels before treatment ($P < 0.05$), but the improvement in these indicators in the research group was much better than that in the control group ($P < 0.05$). In the research group, PR and RP levels after treatment were significantly higher than those before treatment ($P < 0.05$), but patients in the control group showed no obvious changes in PF and RP after treatment ($P > 0.05$; **Table 5**).

Comparison of the adverse reactions

During treatment, the incidence of adverse reactions in the research group was 14.52%, which was slightly higher than the 6.45% recorded in the control group and the difference was not statistically significant ($P > 0.05$; **Table 6**).

Discussion

Vascular dementia is the sole type of dementia with a definite pathogen and effective prophylactic strategy for the early stages. The development of vascular dementia is correlated closely with cerebral ischemia and the dysfunction of oxygen metabolism. Thus, studies of the treatment of vascular dementia have focused on the improvement of blood supply to brain to meet the demands of oxygen metabolism. Butylphthalide soft capsules, a novel type of drug developed in China, ameliorate the blood flow to the brain, antagonizing hypoxic injury in the brain, thrombosis, and platelet coagulation [12]. In this study, we used the medication of butylphthalide soft capsules for the treatment

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Table 3. Comparison of the ADL, MMSE, and CDR scores in both groups ($\bar{x} \pm s$, points)

Group	n	ADL				MMSE				CDR			
		Before treatment	Three months after treatment	t	P	Before treatment	Three months after treatment	t	P	Before treatment	Three months after treatment	t	P
Research group	62	48.62±7.56	82.06±7.39	24.906	0.000	18.17±4.25	22.67±5.02	5.387	0.000	1.83±0.45	1.32±0.28	7.577	0.000
Control group	62	48.02±7.97	55.78±6.82	5.8205	0.000	18.63±4.88	20.15±4.87	2.736	0.035	1.85±0.41	1.46±0.28	6.185	0.000
t	-	0.430	20.578			0.560	2.837			0.430	2.547		
P	-	0.668	0.000			0.577	0.005			0.668	0.012		

Table 5. Comparison of the quality of life scores before and after treatment in both groups ($\bar{x} \pm s$, points)

Group		PF	RP	BP	GH	VT	SF	RE	MH	Total
Research group	Before treatment	43.37±15.16	41.52±10.36	73.65±19.67	35.61±10.64	54.97±11.32	54.71±11.36	48.79±13.95	61.91±12.11	414.53±28.67
	After treatment	58.93±13.74 ^{▲▲}	59.27±11.39 ^{▲▲}	93.54±17.35 ^{▲▲}	43.59±11.21 ^{▲▲}	68.79±12.35 ^{▲▲}	69.51±11.34 ^{▲▲}	78.64±11.83 ^{▲▲}	76.52±10.29 ^{▲▲}	548.79±39.62 ^{▲▲}
Control group	Before treatment	41.35±13.26	38.16±12.25	75.84±21.62	34.51±11.21	55.83±12.11	53.72±12.56	47.63±14.87	60.53±11.24	407.57±26.39
	After treatment	43.51±15.39	41.39±13.68	89.73±17.62 [▲]	38.49±12.03 [▲]	61.78±12.58 [▲]	63.26±13.67 [▲]	72.65±12.15 [▲]	71.63±10.21 [▲]	489.44±21.58 [▲]

Note: [▲]P < 0.05 vs. the level before treatment; ^{▲▲}P < 0.05 vs. the control group.

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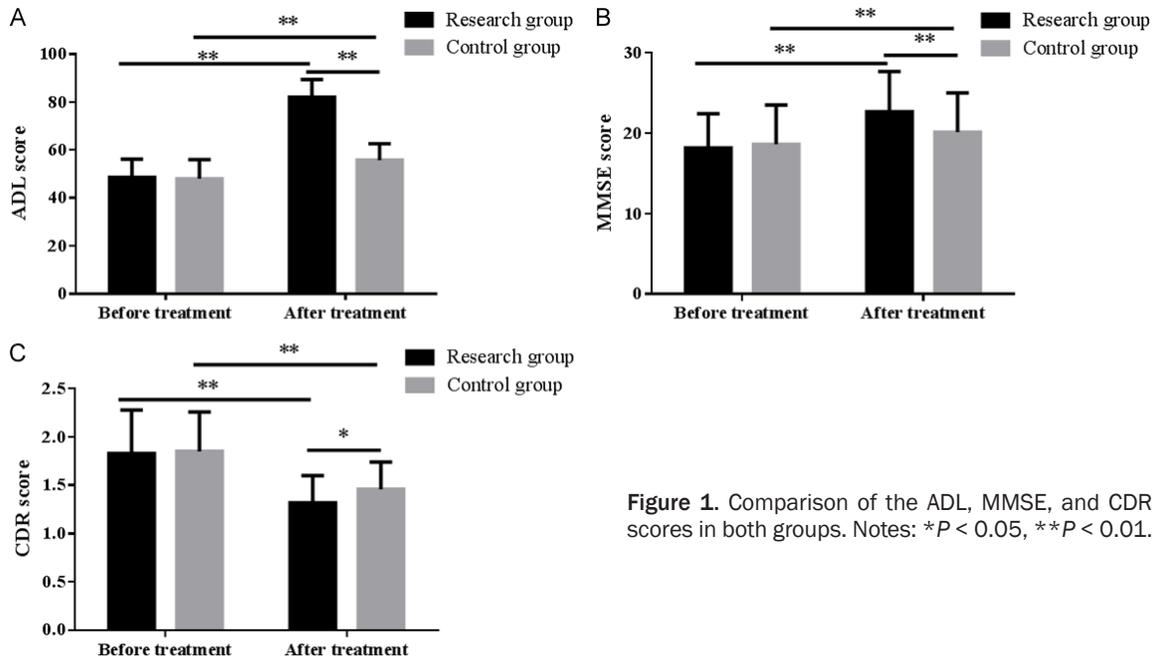


Figure 1. Comparison of the ADL, MMSE, and CDR scores in both groups. Notes: * $P < 0.05$, ** $P < 0.01$.

Table 4. Comparison of the SOD activity and MDA level before and after treatment in both groups ($\bar{x} \pm s$)

Group	n	SOD (nU/ml)				MDA (nmol/ml)			
		Before treatment	3 months after treatment	t	P	Before treatment	3 months after treatment	t	P
Research group	62	74.23±8.56	122.82±10.97	27.496	0.000	6.15±0.97	3.21±1.04	53.667	0.000
Control group	62	74.64±8.42	77.68±10.45	1.784	0.077	6.09±1.03	5.45±1.12	3.312	0.001
t		0.269	23.460			0.334	11.540		
P		0.789	0.000			0.739	0.000		

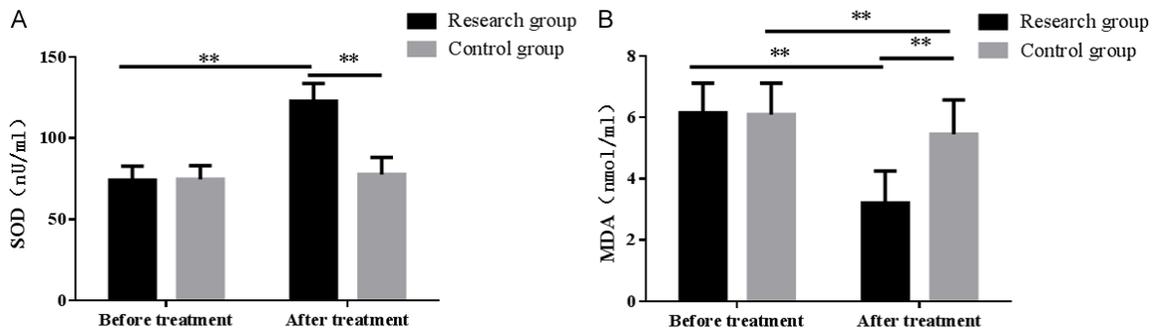


Figure 2. Comparison of the SOD activity and MDA level in both groups before and after treatment. Notes: ** $P < 0.01$.

of patients with vascular dementia. The results showed that butylphthalide improved the cognitive function and quality of life of patients, with promising clinical efficacy and a low incidence rate of adverse reactions.

Butylphthalide soft capsules are a novel medicine developed in China. According to the mod-

ern pharmacology reports [13], butylphthalide soft capsules can antagonize cerebral ischemia through multiple targets. Butylphthalide soft capsules are also reported to reduce the generation of oxygen radicals, thereby relieving the toxicity of oxygen radicals to protect the brain tissues [14]. In addition, butylphthalide soft capsules can regulate the levels of eNOS levels

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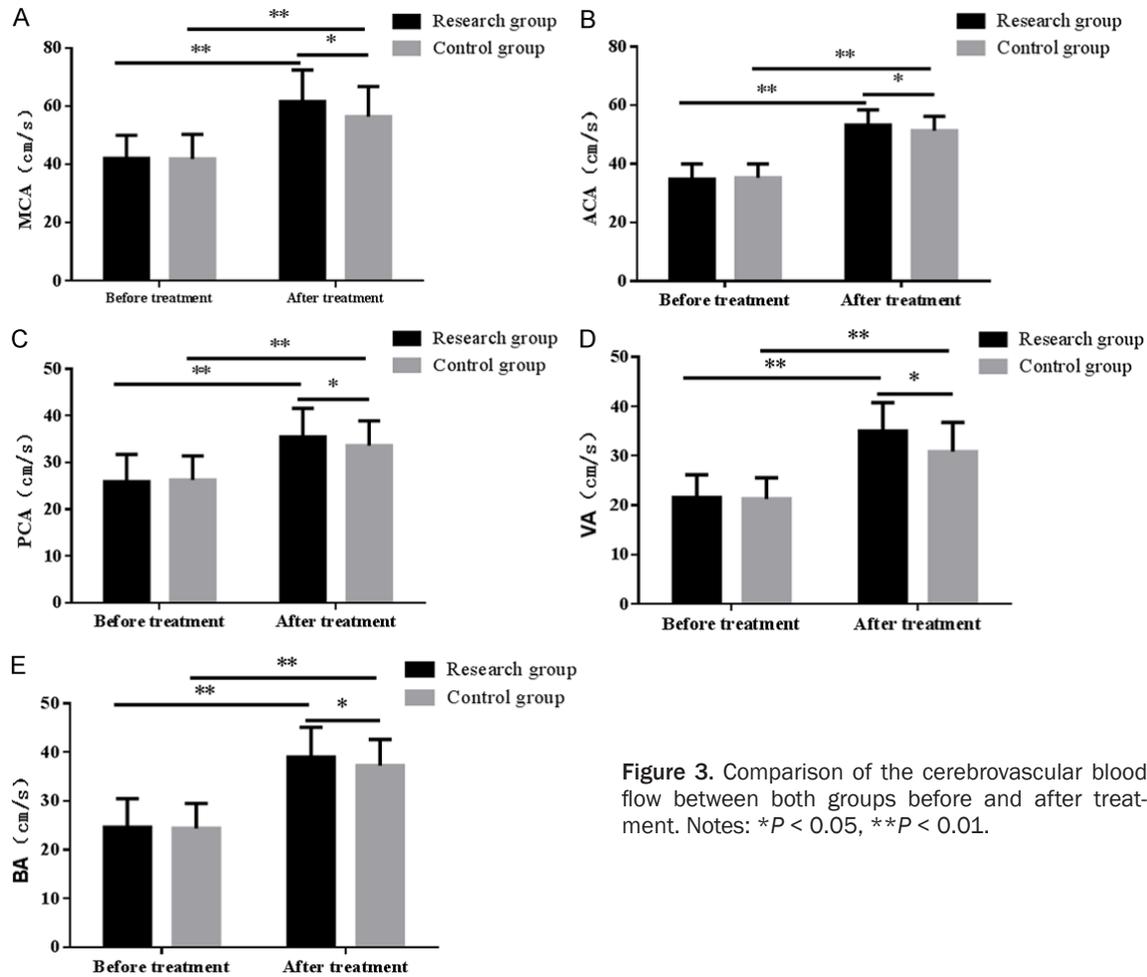


Figure 3. Comparison of the cerebrovascular blood flow between both groups before and after treatment. Notes: * $P < 0.05$, ** $P < 0.01$.

Table 6. Comparison of the adverse reactions in both groups (n, %)

Group	n	Increased transaminase	Nausea	Discomfort in stomach	Nose obstruction	Insomnia	Rash	Total incidence rate
Research group	62	2	2	1	1	1	2	9 (14.52)
Control group	62	0	3	1	0	0	0	4 (6.45)
χ^2	-	2.033	0.208	0.000	1.008	1.008	2.033	2.148
P	-	0.496	1.000	1.000	1.000	1.000	0.496	0.143

and prostaglandin to improve the vascular endothelial functions and prevent the apoptosis of nerve cells [15]. Arachidonic acid and its metabolite can mediate the pathological process of vascular dementia, whereas butylphthalide can interact specifically with this pathological process mediated by arachidonic acid and its metabolite to alleviate vascular spasms and prevent the adhesion and aggregation of platelets inside the vessels, which prevents and improves cerebral ischemia and delays the vascular dementia [16, 17]. In addition, the

results of this study indicated that for patients in the research group, the total effectiveness rate was higher than that in the control group, with more significant improvements recorded in ADL and MMSE scores. Moreover, patients in the research group had a better score for severity assessment of vascular dementia than those in the control group, which is in agreement with the results of previous studies [18] and suggested that butylphthalide soft capsules could mitigate the conditions of vascular dementia and nerve function deficiency, and

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improve daily living activities. Nevertheless, patients in both groups showed similar results in the incidence of adverse reactions, most of which were transient and mild. Thus, butylphthalide soft capsules were confirmed to be safe in clinical practice.

The enzyme SOD has anti-oxygen radical activity; higher SOD activity is suggestive of a more potent ability to eradicate oxygen radicals and mitigate their toxicity [19]. MDA, the toxic metabolite of lipid metabolism, can reflect the extent of damage by oxygen radicals to the brain cells [20]. The results of this study also suggested that after the 3 month treatment period, the SOD activity in the research group was higher than that before treatment, but it was not significantly different from the control group before and after treatment. The MDA levels in both groups were lower than those before treatment and in the research group, the level of MDA after treatment was also lower than that in the control group in the same period. These results suggested that butylphthalide soft capsules increased the activity of SOD, thereby enhancing the ability to eradicate the oxygen radicals and minimizing the generation of MDA. Thus, this action may be the mechanism through which butylphthalide soft capsules treat vascular dementia.

Furthermore, monitoring of the changes in the blood flow in the brains via TCD showed that the blood flow in the MCA, ACA, PCA, VA, and BA in both groups after 3 months of treatment was higher in all arteries than that before treatment. In addition, patients in the research group exhibited more significant increases than in the control group. Thus, butylphthalide soft capsules were shown to significantly increase blood flow in the brain and ameliorate cerebral ischemia, which alleviated the symptoms of dementia.

Although this study showed the therapeutic effect of butylphthalide on vascular dementia, and achieved certain conclusions, there are some limitations. First, the clinical research is limited to one hospital, no multi-center clinical research, and the next step of the study should include more research centers and the number of subjects should be increased to verify the accuracy of the treatment. Secondly, the study used butylphthalide treatment for a short period of time, and no large-scale long-term treat-

ment study was performed. The current study is therefore limited because vascular dementia is a chronic disease. The treatment cycle and observation time should be increased to confirm the long-term efficacy of butylphthalide. Finally, the mechanism of butylphthalide in the treatment of vascular dementia is discussed. However, it is limited to the detection of some serological indicators. Further, animal experiments should be carried out to study the specific signaling pathways of its effects, providing a theoretical basis for the treatment of vascular dementia.

In conclusion, butylphthalide soft capsules can ameliorate the nerve function, cognitive function, daily living activities, and quality of life of patients with vascular dementia. The treatment has a low incidence of adverse reactions and high safety. The mechanism of butylphthalide soft capsules in the treatment of vascular dementia may be associated with an improved blood flow in the brain and reduced oxidative stress in brain tissues. However, a larger number of patients are required to confirm the conclusions of this study.

Disclosure of conflict of interest

None.

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