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Effect of butylphthalide combined with idebenone on vascular dementia

A retrospective observational analysis

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Abstract

To explore the efficacy and safety of butylphthalide combined with idebenone in the treatment of vascular dementia. The clinical data of 126 patients with vascular dementia who were admitted to our hospital between March 2021 and February 2023 were retrospectively reviewed. Among them, 62 patients received butylphthalide alone (single group) and 64 patients received butylphthalide combined with idebenone (combined group). Cognitive function scores, serum inflammatory factor levels, oxidative stress index levels, and incidence of adverse reactions were compared between the 2 groups before and after treatment. After treatment, the Hasegawa Dementia Scale, Mini Mental State Examination Scale, and activities of daily living scores in both groups were higher than before treatment, and the scores in the combined group were higher than before treatment ($P < .05$). After treatment, the levels of serum C-reactive protein, tumor necrosis factor-α, and interleukin 6 in both groups were lower than those before treatment, and those in the combined group were lower than those in the simple group ($P < .05$). After treatment, the levels of serum glutathione peroxidase and superoxide dismutase in the 2 groups were higher than those before treatment, and the level of malondialdehyde was lower than that before treatment. The levels of serum glutathione peroxidase and superoxide dismutase in the combined group were higher than those in the simple group, and the level of malondialdehyde was lower than that in the simple group ($P < .05$). There was no significant difference in the incidence of adverse reactions between the combined group (6.25%) and the simple group (3.23%) ($P > .05$). Compared with butylphthalide alone, intervention of butylphthalide combined with idebenone on vascular dementia can effectively reduce the degree of inflammatory and oxidative stress reactions, improve cognitive function, and promote the ability to perform activities of daily living in a safe manner.

Abbreviations: ADL = activities of daily living, CRP = C-reactive protein, GSH-PX = glutathione peroxidase, HDS = Hasegawa Dementia Scale, IL-6 = interleukin 6, MDA = malondialdehyde, MMSE = Mini Mental State Examination Scale, SOD = superoxide dismutase, TNF-α = tumor necrosis factor-α.

Keywords: butylphthalide, idebenone, vascular dementia

1. Introduction

Vascular dementia is caused by chronic brain injury due to cerebral artery disease.[1,2] Patients often experience a certain degree of behavioral changes, decreased attention and memory, and cognitive impairment.[2,3] If the patient does not receive timely and effective intervention, the neurological function will be further affected as the condition progresses, leading to motor, sensory, and perceptual disorders, which greatly affects the patient's quality of life.[1–3]

Currently, butylphthalide is commonly used in clinical practice to treat patients with vascular dementia. It has a certain vasodilatory effect, can effectively regulate the blood circulation status of the cardiovascular and cerebrovascular systems, increases the blood flow of the cerebral blood supply arteries, and regulates mitochondrial function.[4–6] However, butylphthalide has a relatively single target, and individual treatment effects for patients with vascular dementia vary greatly.[6,7] Some patients may show poor results after receiving only butylphthalide treatment. Therefore, safe and effective treatment of vascular dementia is still a research hotspot.[7] Idebenone is also an important drug for the clinical treatment of cerebrovascular disease, as it can eliminate oxygen free radicals, resist oxidation, enhance the respiratory activity of brain mitochondria, and improve brain function and metabolic status.[8,9]

Literature on the treatment of vascular dementia with butylphthalide and idebenone is limited. Our hospital has

The authors have no conflicts of interest to disclose.

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

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Our study was approved by the Ethics Review Board of Cangzhou Central Hospital [2022-085-2(z)].

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adopted this treatment plan in the past 3 years. Therefore, the records of vascular dementia patients treated in our hospital were retrospectively reviewed to observe the therapeutic effect and safety of butylphthalide combined with idebenone so as to provide a reference for clinical intervention of vascular dementia.

2. Materials and methods

We retrospectively reviewed the clinical data of 126 patients with vascular dementia who were treated at our hospital from March 2021 to February 2023. Among them, there are 73 males and 53 females; age range from 53 to 83 years, with an average age of 67.3 ± 7.0 years; The course of the disease is 1 to 4 years, with a median of 2 (1,2) years. Among them, 62 patients received simple treatment with butylphthalide alone (simple group) and 64 patients were treated with butylphthalide combined with idebenone (combined group).

Inclusion criteria:

- Patients met the diagnostic criteria for vascular dementia[10];
- Patients treated with butylphthalide alone or in combination with idebenone for 3 months.
- Patients who were not treated with anti-dementia drugs within 1 month before this study.
- The clinical data is complete.

Exclusion criteria:

- Patients with hemorrhagic stroke;
- Individuals with dementia caused by other factors;
- Individuals allergic to butylphthalide or idebenone;
- Those who have a history of drug and alcohol dependence;
- Individuals whose cognitive function evaluation was affected by anxiety and depression;
- Patients with acute infection;
- Patients with significant aphasia, visual and auditory impairment.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution and/or the National Research Council and the Declaration of Helsinki (revised in 2013). Written informed consent was obtained from the patients or their legal guardians. The medical ethics committee of our hospital approved this study after obtaining written informed consent from patients or legal guardians.

Treatment methods: (1) Single group: Patients in the single group were given butylphthalide soft capsules (Shijiazhuang Pharma Group Enbipu Pharmaceutical Co., Ltd., Shijiazhuang, Hebei; specification: 0.1 g/tablet; approval number: H20050299) orally 0.2 g/time and 3 times/day. (2) Combined group: Patients in the combined group were given butylphthalide soft capsules combined with idebenone. The treatment of butylphthalide was the same as the single group. Idebenone (Shenzhen Haiwang Pharmaceutical Co., Ltd., Shenzhen; specification: 30 mg/tablet; approval number: H10970363) were given orally 30 mg/time and 3 times/day. Patients in both groups were treated for 3 months.

Outcome measures: (1) Hasegawa Dementia Scale (HDS), Mini Mental State Examination Scale (MMSE), and activities of daily living (ADL) scores before and 3 months after treatment. The HDS score range is 0 to 32.5 points, and the higher the score, the better The MMSE score range is 0 to 30 points, and the higher the score, the better the ability of activities of daily living was evaluated according to the ADL scale, and the score ranged from 0 to 100. The higher the score, the better is the score. (2) Levels of serum inflammatory factors were measured before and 3 months after treatment. Peripheral venous blood (4 mL) was collected and centrifuged. C-reactive protein (CRP) levels were measured using nephelometry, and serum tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) levels were measured using an enzyme-linked immunosorbent assay. (3) Levels of oxidative stress indicators were calculated before and 3 months after treatment in both groups, blood samples were extracted and centrifuged, and the levels of glutathione peroxidase (GSH-PX), malondialdehyde (MDA), and superoxide dismutase (SOD) were determined using enzyme-linked immunosorbent assay. The reagent kit was purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai. (4) The incidence of adverse reactions.

Statistical methods: All data analyses were conducted using SPSS software (version 25.0; IBM Corp, Armonk, NY). The normality of the data was evaluated using the Shapiro–Wilk test. Normally distributed data were expressed as the mean ± standard deviation. The independent sample *t* test was used for inter-group comparisons, and the paired *t* test was used for intragroup comparisons. Data of non-normal distribution were expressed as median and interquartile interval. The Mann–Whitney *U* test was used for inter-group comparisons, and the Wilcoxon signed-rank test was used for intra-group comparisons. Counting data were represented by the number of cases, and Chi-squared test was used. Differences were considered statistically significant at $P < .05$.

3. Results

There was no significant difference in the baseline data between the 2 groups ($P > .05$) (Table 1).

Before treatment, there was no significant difference in HDS, MMSE, and ADL scores between the 2 groups ($P > .05$); After treatment, the HDS, MMSE, and ADL scores of the 2 groups increased compared to before treatment, and the combined group was higher than the simple group ($P < .05$) (Table 2).

Before treatment, there was no significant difference in serum inflammatory factor levels between the 2 groups ($P > .05$). After treatment, the levels of serum CRP, TNF-α, and IL-6 in both groups decreased compared to before treatment, and the combined group was lower than that in the simple group ($P < .05$) (Table 3).

Table 1

Comparison of baseline data of the patients.

Group	Gender (male/female)	Age (years)	Course of disease (years)	Education level	
				Below high school	High school and above
Combined group (n = 64)	39/25	67.8 ± 6.7	2 (1, 2)	34	30
Simple group (n = 62)	34/28	66.8 ± 7.3	2 (1, 3)	28	34
$\chi^2/t/Z$	0.481*	0.759†	−0.793‡	0.799*	
P	.488	.450	.428	.371	

*Chi-square test.

†*t*-test.

‡Mann–Whitney U test.

Table 2

Comparison of cognitive function and activities of daily living ability scores between the 2 groups (points).

Time	Group	n	HDS	MMSE	ADL
Before treatment	Combined group	64	15.5 ± 2.6	15 (14, 18)	54.2 ± 6.2
	Simple group	62	16.3 ± 3.0	16 (15, 19)	55.3 ± 7.0
	t/Z		–1.729†	–1.490‡	–0.908†
	P		.086	.136	.366
After treatment	Combined group	64	24.8 ± 2.9*	24 (23, 27)*	79.4 ± 6.5*
	Simple group	62	20.2 ± 3.1*	22 (21, 24)*	73.2 ± 6.9*
	t/Z		8.667†	–4.902‡	5.248†
	P		<.001	<.001	<.001

Note: Compared with before treatment in this group.
*$P < .05$.
†*t*-test.
‡Mann–Whitney *U* test.

Table 3

Comparison of serum inflammatory factor levels between 2 groups.

Time	Group	n	CRP (mg/L)	TNF-α (ng/L)	IL-6 (ng/L)
Before treatment	Combined group	64	8.04 ± 0.76	170.2 ± 17.7	34.3 ± 7.81
	Simple group	62	7.89 ± 0.72	170.9 ± 18.5	33.0 ± 5.1
	t		1.092	–0.232	1.525
	P		.277	.817	.130
After treatment	Combined group	64	3.10 ± 0.57*	101.3 ± 14.4*	12.3 ± 3.7*
	Simple group	62	3.86 ± 0.64*	117.4 ± 13.9*	16.1 ± 4.1*
	t		–7.040	–6.361	–5.482
	P		<.001	<.001	<.001

Note: Compared with before treatment in this group.
*$P < .05$.

Before treatment, there was no significant difference in the levels of serum oxidative stress indicators between the 2 groups ($P > .05$); After treatment, the serum levels of GSH-PX and SOD in both groups increased compared to before treatment, while MDA levels decreased compared to before treatment. Moreover, the serum GSH-PX and SOD levels in the combination group were higher than those in the simple group, while the MDA levels were lower than those in the simple group ($P < .05$) (Table 4).

There was no significant difference in the incidence of adverse reactions between the combination (6.25%) and simple groups (3.23%) ($P > .05$) (Table 5).

4. Discussion

This study showed that the combination of butylphthalide and idebenone in the treatment of vascular dementia is safe and effective, which can effectively improve the cognitive function of patients, alleviate clinical symptoms, and help improve their ability to perform activities of daily living. The main reason is that butylphthalide can scavenge oxygen free radicals, regulate cerebral collateral circulation, rebuild microcirculation in ischemic areas, and improve neural cell function.[11] Idebenone is a Coenzyme Q10 analog that regulates brain function metabolism. It can improve the stability of the mitochondrial membrane, strengthen the respiratory activity of brain mitochondria, regulate the energy metabolism of cerebral ischemia, and play a synergistic role in combination with butylphthalide to effectively improve the cognitive function of patients.[12] Gao L et al[13] confirmed through animal experiments that the main active component of butylphthalide is racemic 3-n-butylphthalide, which can improve mitochondrial function and inhibit glutamate generation, thereby increasing the content of PGI2 and NP in the brain vascular endothelium, downregulating the content of arachidonic acid and calcium ions in cells, alleviating cerebral ischemic memory dysfunction, and restoring neural function. Meanwhile, butylphthalide can increase the levels of vascular endothelial growth factor and heme oxidase in the ischemic cortex and hippocampus, inhibit the degeneration and death of hippocampal neurons, and reduce the degree of cognitive dysfunction.[14] Qian X et al[15] reported that idebenone is a brain metabolic activator with strong antioxidant function and is also an intelligent promoter, which is of great significance in improving cognitive function. Qi et al[16] confirmed that the combination of butylphthalide and idebenone in the treatment of patients with vascular dementia can effectively improve their cognitive function and activities of daily living and reduce the degree of dementia, which is consistent with the results of this study. Their research also showed that the combined treatment of butylphthalide and idebenone can avoid the massive production of oxygen free radicals, maintain the content of adenosine triphosphate required by normal cells and the energy metabolism required by cell ischemia, improve the utilization rate of glucose in the brain, and ensure the improvement of cognitive function.[16]

Oxidative stress and inflammatory responses also play an important role in the pathogenesis and progression of vascular dementia.[17,18] Overproduction of oxygen free radicals can cause lipid peroxidation of unsaturated fatty acids in the cell membrane, which can lead to functional damage, aging, and apoptosis of nerve cells, leading to memory and cognitive dysfunction. Research has shown that GSH-PX and SOD are important antioxidant enzymes in the body and scavengers of oxygen free radicals, whereas MDA is a product of lipid peroxidation caused by the action of free radicals. Serum levels are closely related to the level of oxygen free radicals and the degree of the oxidative stress response.[19] CRP, TNF-α, and IL-6 can directly damage blood vessels, exacerbate cerebrovascular diseases, and in severe cases cause neuronal apoptosis and intellectual decline, leading

Table 4

Comparison of levels of oxidative stress indicators between 2 groups.

Time	Group	n	GSH-PX (U/mL)	MDA (μmol/L)	SOD (U/mL)
Before treatment	Combined group	64	77.5 ± 8.8	8.25 ± 1.39	75.1 ± 9.5
	Simple group	62	76.6 ± 9.1	8.51 ± 1.35	74.3 ± 9.1
	t		0.603	−1.057	0.484
	P		.547	.293	.629
After treatment	Combined group	64	94.5 ± 7.8*	5.59 ± 1.10*	90.3 ± 10.9*
	Simple group	62	87.1 ± 8.9*	6.70 ± 1.24*	81.9 ± 8.7*
	t		4.949	−5.287	4.806
	P		<.001	<.001	<.001

Note: Compared with before treatment in this group.
*$P < .05$.

Table 5

Comparison of adverse reaction rates between 2 groups.

Group	n	Vomit	Headache	Rash	Total occurrence rate
Combined group	64	1 (1.56)	2 (3.13)	1 (1.56)	4 (6.25)
Simple group	62	1 (1.61)	1 (1.61)	0 (0.00)	2 (3.23)
χ^2					0.143
P					0.705

to varying degrees of dementia. The results of this study indicate that after treatment, the serum CRP, TNF-α, IL-6, GSH-PX, and SOD levels in the combination group were higher than those in the simple group, whereas MDA levels were lower than those in the simple group.[20] It is suggested that butylphthalide combined with idebenone may also help to reduce the degree of inflammatory reaction and oxidative stress in patients with vascular dementia, mainly because butylphthalide can protect mitochondria, increase the content of Prostacyclin and nitric oxide in cerebral vascular endothelium, prevent the generation of glutamic acid, clean up oxygen free radicals, enhance the activity of antioxidant enzymes, and reduce the level of inflammatory factors. As a brain protective agent, idebenone can also eliminate oxygen free radicals, promote lipid peroxidation, enhance the respiratory activity of brain mitochondria, regulate brain energy metabolism, and achieve the purpose of alleviating inflammation and stress response.[21,22]

In addition, we found that the safety profile of the combined therapy was comparable to that of butylphthalide alone, which suggests that the combination of butylphthalide and idebenone is safe, which is consistent with the findings by Qi et al.[16]

Limitations: The study is a single-center retrospective analysis with small sample size, which may have selection bias. The observation time was relatively short, and its exact efficacy and safety need to be further studied and confirmed by prospective studies with larger sample size. Moreover, all types of vascular dementia were included in this study, which may affect the results of study. The effects of butylphthalide combined with idebenone on each type should be further studied to confirm the results of our findings.

5. Conclusion

Compared with butylphthalide alone, intervention of butylphthalide combined with idebenone on vascular dementia can effectively reduce the degree of inflammatory reaction and oxidative stress reaction, improve cognitive function, and promote the ability of activities of daily living in a safe manner.

Author contributions

Conceptualization: Hongxia Zhang.
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