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Original Article

Effects of butylphthalide soft capsules on cognitive function, ability of daily living, and related factors in patients with Parkinson's disease dementia

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Abstract: Objective: This paper aimed to explore the clinical efficacy of butylphthalide soft capsules (BSC) on treating Parkinson's disease dementia (PDD). Methods: Ninety-two patients with PDD were randomly divided into a control group (46 cases, who were orally administered donepezil tablets before bedtime) and an experimental group (46 cases, treated with donepezil tablets and BSC). Both groups were treated for 16 weeks. They were compared in terms of their effective rates of treatment, pre- and post-treatment scores of UPDRS, MoCA, MMSE, and ADL, and pre- and post-treatment levels of serum CRP, CysC, and PARK7. The occurrence of adverse reactions (such as dizziness, nausea and vomiting, and fatigue) during the treatment was observed. Results: The effective rate of treatment was higher in the experimental group than that in the control group (93.48% VS 73.91%) ($P<0.05$). After treatment, scores of MoCA, MMSE, and ADL all increased ($P<0.01$ or $P<0.001$), while UPDRS scores and levels of serum CRP, CysC, and PARK7 all decreased in the two groups (all $P<0.001$). Moreover, the increase and the decrease in the experimental group were greater than those in the control group (all $P<0.001$). The difference was not statistically significant in the incidence of adverse reactions between the control and experimental groups (8.70% VS 6.52%) ($P>0.05$). Conclusion: BSC has a definite curative effect in treating PDD, with high safety. It can improve the patients' cognitive function, reduce their level of related factors, and enhance their ability of daily living, so it is worthy of promotion.

Keywords: Butylphthalide soft capsules, cognitive function, Parkinson's disease, dementia, ability of daily living, inflammatory cytokines

Introduction

Parkinson's disease (PD) is a common disease in the elderly, and its clinical manifestations are mainly muscular rigidity and resting tremor [1-4]. With a high incidence, the disease seriously affects the quality of life. If it continues to progress, nearly 40% of the patients suffer from personality changes, memory loss, and cognitive impairment, and eventually experience Parkinson's disease dementia (PDD) [5-8]. PDD seriously reduces the patients' motor and cognitive functions, then causes a loss of ability in daily living, and finally brings a heavy burden to the family and society [1]. In clinical practice PDD is usually treated by dopaminergic agents [9]. Although dopaminergic agents can relieve the clinical symptoms of the patients, the agents cause certain adverse reactions and lead to a poor prognosis. Therefore, how to treat the disease more safely and effectively has become a hot topic in neurology for the past few years. According to a previous study, inflammatory and oxidative stress responses in the body exert an important function in the development and progression of PDD, so effectively reducing the two responses is particularly significant to improve patients' conditions [10]. Accordingly, patients with PDD were treated with butylphthalide soft capsules (BSC) in this study, and the mechanism of action of this drug was explored through observing pre- and post-treatment changes in indicators (CRP, CysC, PARK7) related to the two responses. The report is as follows.

Materials and methods

General information

Ninety-two patients with PDD admitted to Taizhou First People's Hospital were enrolled as

research subjects, and the time of investigation was from March 2017 to April 2019. The patients were divided into the control group (46 cases, orally administrated with donepezil tablets before bedtime) and the experimental group (46 cases, treated with donepezil tablets and BSC) based on a random number table.

Enrollment criteria were as follows: all patients met the relevant diagnostic criteria of *Guidelines for Diagnosis and Treatment of Parkinson's Disease Dementia*; patients had good compliance and cooperation in the research; patients were aged 60-90 years old.

Exclusion criteria were as follows: patients with dementia caused by other types of diseases and patients with cognitive impairment caused by other factors; patients who had received relevant treatment within 3 months before enrollment, and patients who were allergic to the drugs used in this study; patients with a history or a family history of epilepsy.

The control group consisted of 21 females and 25 males, who were aged 61-89 years old, with an average age of (68.9±4.6) years, a course of disease of 2-13 years, and an average course of disease of (7.69±2.18) years. Based on the Hoehn-Yahr staging, there were 13 cases of grade II, 12 cases of grade III, 11 cases of grade IV, and 10 cases of grade V in this group [11]. The experimental group consisted of 20 females and 26 males, who were aged 60-87 years old, with an average age of (68.5±4.3) years, a course of disease of 1-15 years, and an average course of disease of (7.92±2.21) years. Based on the Hoehn-Yahr staging, there were 14 cases of grade II, 11 cases of grade III, 13 cases of grade IV, and 8 cases of grade V. The differences were not statistically significant between the two groups in their general information, which indicated group comparability (P>0.05). The patients' family members signed an informed consent form. This study was approved by the Medical Ethics Committee of Taizhou First People's Hospital.

Methods

After admission, the patients in both groups received anti-depression and other routine treatments. Additionally, those in the control group were orally administrated with donepezil tablets (Shanxi Fangzhou Pharmaceutical Co., Ltd.) before bedtime, one tablet/time and once daily. After 4-weeks of treatment, the dosage was changed to 2 tablets/time and once daily for 16-week treatment. In addition to the oral donepezil tablets, those in the experimental group were orally administrated with BSC (CSPC NBP Pharmaceutical Co., Ltd.) for 16 weeks, 0.2 g/time and twice daily.

Outcome measures

Patients in the control and experimental groups were compared with respect to clinical efficacy, pre- and post-treatment changes in mental states, cognitive function, daily living ability, and related serum factors, and the incidence of adverse reactions. (1) Clinical efficacy. Based on *Diagnosis and Efficacy Evaluation Criteria for Alzheimer's Disease*, the efficacy evaluation criteria were formulated: markedly effective indicated that the symptoms disappeared, and the patients could take care of themselves in daily life; effective indicated that the symptoms were relieved, and the patients could partially take care of themselves; ineffective indicated that the above criteria were not met [12]. Total effective rate = (markedly effective + effective cases)/total number of cases × 100%. (2) Disease control. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess the patients' disease control from their spirit, behavior and emotion, and daily activity and motor function [13]. The score of each item was divided into 5 grades (0-4 points). Lower scores indicated better disease control. (3) Mental states. The Mini-Mental State Examination (MMSE) was used to assess the patients' mental states, including calculation, attention, orientation, etc., with a full score of 30 points [14]. The mental states were normal if illiterate patients had a score ≥17 points, patients graduating from primary school had a score ≥20 points, and patients graduating from junior high school and above had a score ≥24 points. Higher scores indicated better mental states. (4) Cognitive function. The Montreal Cognitive Assessment (MoCA) was used to assess the patients' cognitive functions, including language, memory, execution, and other aspects, with a full score of 30 points [15]. A score ≥26 points indicated no cognitive impairment, a score between 21-25 points indicated mild cognitive impairment, and a score <21 points indicated dementia. The MoCA scores were

Table 1. Comparison of general information between two groups (n, $\bar{x}$ ± sd)

Group	Control group (n=46)	Experimental group (n=46)	χ^2/t/Z	P
Gender (case)			0.044	0.834
Male	25	26		
Female	21	20		
Age (year)	68.9±4.6	68.5±4.3	0.431	0.668
Course of disease (year)	7.69±2.18	7.92±2.21	0.503	0.617
Hoehn-Yahr staging (case)			-0.271	0.787
Grade II	13	14		
Grade III	12	11		
Grade IV	11	13		
Grade V	10	8		

Table 2. Comparison of effective rates of treatment between two groups (n, %)

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=46)	19 (41.30)	15 (32.61)	12 (26.09)	34 (73.91)
Experimental group (n=46)	30 (65.22)	13 (28.26)	3 (6.52)	43 (93.48)
χ^2				6.452
P				0.011

positively correlated with the cognitive functions. (5) Abilities of daily living. The Activities of Daily Living Scale (ADL) was used to assess the patients' ability of daily living [16]. A score <19 points indicated that the patients could not take care of themselves in daily life; a score between 20-39 points indicated that the patients needed help from others; a score between 40-59 points indicated that the patients could partially take care of themselves, but they still needed help in some aspects; a score ≥60 points indicated that the patients could basically take care of themselves. (6) Related serum factors. Before and 16 weeks after treatment, fasting venous blood from the elbow (5mL) was drawn from patients in both groups. After centrifugation of the blood, serum was collected to measure levels of C-reactive protein (CRP) and cystatin C (CysC) using immunoturbidimetry. The levels were then compared. PARK7 levels were determined by enzyme-linked immunosorbent assay (ELISA). The kits of the three factors were purchased from Shanghai Kang Lang Biological Technology Co., Ltd. (180911, 190218, 190412), and the operating steps were carried out in strict accordance with the kit instructions. (7) Adverse reactions. Adverse reactions included dizziness, nausea and vomiting, fatigue, etc. were recorded.

Statistical analysis

SPSS 19.0 was used to process the data. Measurement data conforming to a normal distribution were expressed as ($\bar{x}$ ± sd), and a t test was used for their comparison. Count data (the effective rates of treatment and the incidence of adverse reactions) were expressed as percentage, and a χ^2 test was used for their comparison. When P<0.05, the difference was statistically significant.

Results

General information

This study is a prospective study. A total of 92 PPD patients were included and randomly divided into two groups (n=46 each). During the experiment, no case was dropped or eliminated. The difference was not statistically significant between the control and experimental groups in terms of general data and information (P>0.05, **Table 1**).

Comparison of effective rates of treatment

The effective rates of treatment in the experimental and control groups were 93.48% (43/46) and 73.91% (34/46), respectively. The total effective rate was higher in the experimental group (P<0.05), indicating that BSC can significantly improve the clinical efficacy of treatment for PDD (**Table 2**).

Comparison of UPDRS and MMSE scores before and after treatment

Before treatment, the differences were not significant in UPDRS and MMSE scores between

Table 3. Comparison of UPDRS and MMSE scores before and after treatment ($\bar{x}$ ± sd, score)

Group	Control group (n=46)	Experimental group (n=46)	t	P
UPDRS scores				
Before treatment	47.25±6.57	47.93±5.96	0.520	0.604
After treatment	33.16±5.63	22.53±5.77	8.943	<0.001
t	11.045	20.767		
P	<0.001	<0.001		
MMSE scores				
Before treatment	22.15±3.12	21.36±3.38	1.165	0.247
After treatment	24.12±3.77	27.10±2.69	4.364	<0.001
t	2.730	9.012		
P	0.008	<0.001		

Note: UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination.

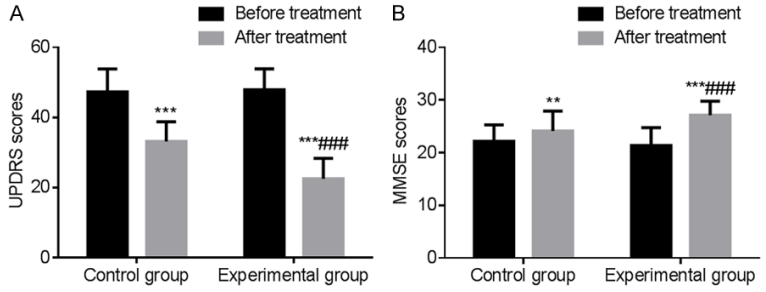

Figure 1. Comparison of UPDRS and MMSE scores before and after treatment. A. Comparison of UPDRS scores before and after treatment; B. Comparison of MMSE scores before and after treatment; Compared with before treatment, **P<0.01, ***P<0.001; Compared with the control group after treatment, ###P<0.001. UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination.

Table 4. Comparison of MoCA and ADL scores before and after treatment ($\bar{x}$ ± sd, score)

Group	Control group (n=46)	Experimental group (n=46)	t	P
MoCA scores				
Before treatment	18.79±4.58	18.26±4.27	0.574	0.567
After treatment	24.26±4.33	28.82±1.18	6.891	<0.001
t	5.886	16.167		
P	<0.001	<0.001		
ADL scores				
Before treatment	59.34±11.14	58.10±10.22	0.556	0.579
After treatment	67.21±10.69	77.20±11.52	4.311	<0.001
t	3.457	8.412		
P	0.001	<0.001		

Note: MoCA: Montreal Cognitive Assessment; ADL: Activity of Daily Living Scale.

the experimental and control groups (both P>0.05). After treatment, the UPDRS scores decreased significantly (both P<0.001), while the MMSE scores increased significantly in both groups (P<0.01 or P<0.001). After treatment, the two scores were better in the experimental group (both P<0.001), indicating that BSC can relieve the clinical symptoms and improve the mental states of patients with PDD (**Table 3** and **Figure 1**).

Comparison of MoCA and ADL scores before and after treatment

Before treatment, the differences were not significant in MoCA and ADL scores between the experimental and control groups (both P>0.05). After treatment, the two scores increased significantly in the two groups (P<0.01 or P<0.001). After treatment, the two scores were better in the experimental group (both P<0.001), indicating that BSC can improve the cognitive function and daily living ability of patients with PDD (**Table 4** and **Figure 2**).

Comparison of serum CRP, PARK7, and CysC levels before and after treatment

Before treatment, the differences were not significant in CRP, PARK7, and CysC levels between the experimental and control groups (all P> 0.05). After treatment, the three levels decreased significantly in both groups (all P<0.001). After treatment, the three levels were lower in the experimental group (all P<0.001), indicating that BSC can improve the expression of serum CRP, PARK7, and CysC in patients with PDD (**Table 5** and **Figure 3**).

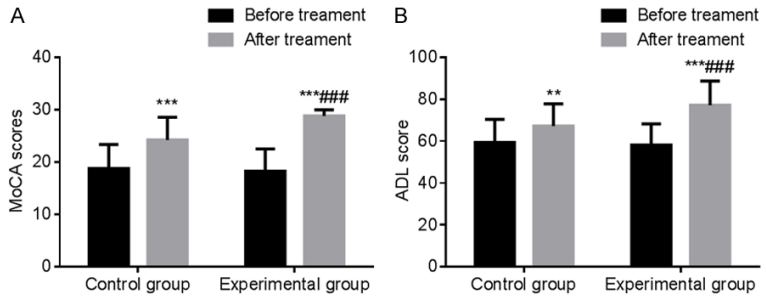

Figure 2. Comparison of MoCA and ADL scores before and after treatment. A. Comparison of MoCA scores before and after treatment; B. Comparison of ADL scores before and after treatment; Compared with before treatment, $^{**}P<0.01$, $^{***}P<0.001$; Compared with the control group after treatment, $^{###}P<0.001$. MoCA: Montreal Cognitive Assessment; ADL: Activity of Daily Living Scale.

Table 5. Comparison of serum CRP, PARK7, and CysC levels before and after treatment $\bar{x} \pm sd$)

Group	Control group (n=46)	Experimental group (n=46)	t	P
CRP (μg/mL)				
Before treatment	8.36±1.04	8.42±0.93	0.292	0.771
After treatment	6.23±0.85	4.15±0.72	12.664	<0.001
t	5.886	16.167		
P	<0.001	<0.001		
CysC (mg/L)				
Before treatment	2.11±0.68	2.05±0.73	0.408	0.684
After treatment	1.51±0.52	1.02±0.34	5.349	<0.001
t	4.754	8.675		
P	<0.001	<0.001		
PARK7 (ng/L)				
Before treatment	32.16±5.10	32.77±4.37	0.616	0.539
After treatment	23.66±4.62	14.20±3.77	10.760	<0.001
t	8.378	9.110		
P	<0.001	<0.001		

Note: CRP: C-reactive protein; CysC: cystatin C.

Comparison of incidence of adverse reactions

The total incidence of adverse reactions was 8.70% in the experimental group and 6.52% in the control group, without a statistically significant difference between the two groups (P>0.05, **Table 6**).

Discussion

As population aging accelerates, the number of patients with PD and PDD has been rising in China. PD is a common clinical disease with a relatively high incidence, and patients with the disease usually suffer from bradykinesia that is complicated with muscle rigidity and other adverse symptoms. Therefore, the delayed treatment of PD easily results in dementia symptoms, reduces the patients' cognitive function, and seriously affects their quality of life [17-19]. With the deepening of clinical research on PDD, studies have shown that the onset of PDD is related to the dysfunction of the ascending cholinergic pathway [20, 21]. In recent years, donepezil hydrochloride tablets are often used to treat PPD in clinical practice [22, 23]. As an acetylcholinesterase inhibitor, this drug can be specifically combined with acetylcholinesterases to improve acetylcholine levels in patients, thus relieving clinical symptoms and improving cognitive function. However, the long-term use of it leads to fatigue, dizziness, and other adverse reactions [24]. Therefore, searching for more effective therapeutic schemes for patients with PDD has become a hot topic in neurology for the past few years.

In recent years, BSC has been gradually applied to the clinical treatment of patients with PD, showing a remarkable effect. In our study, patients in the experimental group had a significantly higher effective rate of treatment, better post-treatment improvement of UPDRS, MoCA, MMSE, and ADL scores, and better tolerance [25]. Additionally, the adverse reactions in the experimental group were slighter, with little difference from those in the control group. This reveals that BSC can control the patients' conditions, improve their cognitive function, and enhance their daily living ability, with remarkable efficacy and few adverse reactions in the treatment of PDD. The reason is as follows: BSC is a racemic n-butylphthalide, and it can protect

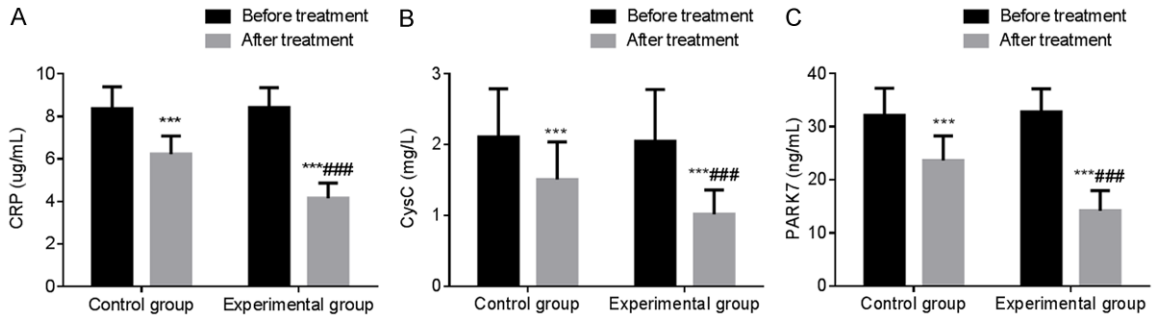

Figure 3. BSC can improve serum CRP, PARK7 and CysC levels in patients with PDD. A. Comparison of CRP levels before and after treatment; B. Comparison of CysC levels before and after treatment; C. Comparison of PARK7 levels before and after treatment; Compared with before treatment, ***P<0.001; Compared with the control group after treatment, ###P<0.001. PDD: Parkinson's disease dementia; CRP: C-reactive protein; CysC: cystatin C.

Table 6. Comparison of incidence of adverse reactions (n, %)

Group	Feel sick and vomit	Dizziness	Insomnia	Tired	Total incidence
Control group (n=46)	1 (2.17)	1 (2.17)	1 (2.17)	0 (0.00)	3 (6.52)
Experimental group (n=46)	2 (4.35)	1 (2.17)	0 (0.00)	1 (2.17)	4 (8.70)
χ^2					0.000
P					0.694

the brain tissue, inhibit the release of glutamate and oxygen free radicals, and reduce damage to neurons, thereby facilitating the neurological functional recovery of patients with PDD. In addition to resisting hypoxia and ischemia in brain cells, this drug can also increase cerebral blood flow, enhance the oxidation of ischemic areas, and relieve symptoms of cerebral edema, further significantly inhibiting the apoptosis of brain cells and the infarction of ischemic areas. Therefore, BSC is beneficial to the recovery of cerebral nerve functions in patients [26]. According to a clinical study, inflammatory responses, oxidative stress responses, and mitochondrial dysfunction are all important pathogenesis of PDD [27]. CRP is a typical inflammatory cytokine, and changes in its levels represent the degree of body inflammatory responses. CysC, also an inflammatory cytokine, is involved in the pathophysiological process of PDD, and changes in its levels are correlated with the cognitive impairment of the patients. PARK7 is an encoded protein that is related to the pathogenesis of PD. It can resist oxidative stress responses, promote proteolytic enzyme function, and mediate the development and progression of PD. In our study, after treatment, the four scores were significantly improved, and the three levels decreased in the experimental group, and the changes were greater compared with the control group. This suggests that BSC can reduce the inflammatory and oxidative stress responses of patients with PDD, relieve their clinical symptoms, and promote their physical recovery.

In summary, BSC has a definite curative effect and high safety in treating PDD. BSC can improve patients' cognitive function, reduce levels of related factors, and enhance daily living ability. It's mechanism of action may be related to the alleviation of inflammatory and oxidative stress responses in the body. However, due to the fact that this study is a single-center study with a small sample size and short observation time, the experimental results may be biased to some extent. Therefore, we will enlarge the sample size, prolong follow-up time, and conduct multi-center studies for further discussion in the future.

Disclosure of conflict of interest

None.

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