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Original Research Article

Effect of a combination of donepezil tablets and butylphthalide soft capsules on neurological function in dementia patients, and its effect on serum inflammatory factors

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Abstract

Purpose: *To determine the effect of combined use of donepezil tablets and butylphthalide soft capsules in the treatment of patients with vascular dementia, and its effect on serum inflammatory factor levels and neurological functional recovery of patients.*
Methods: *120 patients with vascular dementia were selected and assigned to group A (n = 60) and group B (n = 60). All patients were treated with donepezil tablets, while patients in group A were, in addition, treated with butylphthalide soft capsules. Mini mental state examination (MMSE) scores, clinical dementia rating scale (CDRS) scores, activities of daily living (ADL) scores, incidence of adverse reactions, serum inflammatory factor levels and neurological functional recovery were determined.*
Results: *There was significantly higher MMSE score in group A than in B, while CDRS score was lower in group A. The ADL scores and inflammatory factor levels were lower in group A than in B ($p < 0.001$), while neurological functional recovery was markedly better in A ($p < 0.001$). Incidents of unwanted events were comparable in groups A and B, and there were no serious complications in the patients.*
Conclusion: *The combination therapy of donepezil tablets and butylphthalide soft capsules reduces inflammatory factor levels and improved cognitive level and quality of life of patients with vascular dementia. It also produces good neurological functional recovery and low incidence of adverse reactions. Therefore, this treatment strategy has potentials for the management of vascular dementia.*

Keywords: *Vascular dementia, Donepezil tablets, Butylphthalide soft capsules, Neurological function, Inflammatory factors*

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INTRODUCTION

Vascular dementia is also known as vascular cognitive impairment syndrome. Due to decreased cognitive and neurological function in patients with this disease, there are reductions in emotional expression and memory as well. Some patients may have severe executive function

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disorders which exert significant adverse impacts on their daily lives [1-3].

Vascular dementia often occurs in the elderly population. With the growing population of the elderly in China and an increasing number of patients with vascular dementia, this disease has become a difficult problem that needs to be urgently solved in the field of social medicine. At present, the pathogenesis of vascular dementia has not been clearly understood. However, it has been speculated that this disease may be related to cerebral microcirculation and inflammatory response in patients. Therefore, the treatment of the patients should focus on optimizing blood circulation to the brain, and reducing the levels of inflammatory factors so as to provide better conditions for the neurological functional recovery [4-7]. Donepezil tablets and butylphthalide soft capsules are popular drugs used clinically for treating Alzheimer's disease.

Donepezil inhibits the secretion of acetylcholinesterase and reduces cognitive impairment in patients. Butylphthalide soft capsules mitigates brain hypoxia, promotes cerebral microcirculation and shortens the process involved in neurological rehabilitation [8-10]. Clinical studies have shown that the use of donepezil tablets as sole drug is not very effective. Therefore, this study was carried out to investigate the effect of combination of donepezil tablets and butylphthalide soft capsules in the treatment of vascular dementia patients.

EXPERIMENTAL

General data of patients

The subjects used comprised 120 vascular dementia in-patients who were assigned equally to 2 groups (A and B) according to the order of admission. Patients' profiles in the 2 groups were similar. The research received approval from the ethical committee of Tongwei County Hospital of Traditional Chinese Medicine (approval no. 20181137*)*, and its implementation followed the guidelines of Declaration of Helsinki [11]. The protocol involved in the study was explained to the subjects and guardians, and written consent was obtained from them.

Inclusion criteria

Patients diagnosed with vascular dementia through examination and the diagnostic criteria of the Swiss International Society for Neuroscience Research [12], and patients who could cooperate during the research, were included.

Exclusion criteria

Mentally-challenged patients, patients with impaired communication ability; those with other organic illnesses; patients who had a history of consciousness disorder, epilepsy and mental disorder; patients with dementia caused by other diseases; patients with severe cardiovascular diseases; and patients who had taken drugs that affect cognition within 3 months before the study, were excluded.

Treatments

Both groups received conventional treatment and donepezil tablets. The patients were given 5 mg of donepezil tablets (Tianjin Lisheng Pharmaceutical Co. Ltd.; NMPA approval No. H20040745), once a day, for 6 months. In addition, patients in group A were given 0.2 g of butylphthalide soft capsules (CSPC NBP Pharmaceutical Co. Ltd.; NMPA approval no. H20050299), three times a day, for 6 months.

Table 1: Comparison of patients' profiles

Variable	Group A (n=60)	Group B (n=60)	χ^2/t	*P*-value
Gender			0.033	0.855
Male	30	31		
Female	30	29		
Mean age (years)	71.21±6.20	71.23±6.21	0.018	0.986
Mean disease duration (years)	2.22±0.56	2.31±0.54	0.896	0.372
Education level (years)	8.22±2.12	8.23±2.23	0.025	0.980
Hypertension	20	21	0.037	0.847
Coronary heart disease	12	11	0.054	0.817
Pulmonary disease	5	6	0.100	0.752
Smoking history	15	16	0.044	0.835
Drinking history	22	21	0.036	0.849
Cognitive assessment scale scores (points)	18.21±5.65	18.32±5.54	0.108	0.914

Evaluation of treatment indices

Mini-mental state examination (MMSE) score

Mental recovery was compared between the patients, based on MMSE score. The higher the score, the higher the cognitive level. The time nodes for comparison were pre-therapy, 3 months post-therapy, and 6 months post-therapy [13].

Clinical dementia rating scale (CDRS) score

Dementia was evaluated based on CDRS scores. The higher the CDRS score, the more severe the dementia. The time nodes for comparison were pre-therapy, 3 months post-therapy and 6 months post-therapy [14].

Activities of daily living (ADL) score

The ADL was used to evaluate the activities of daily living. The lower the score, the better the patient's ability of daily living. The time nodes for comparison were pre-therapy, 3 months post-therapy and 6 months post-therapy [15].

Incidence of adverse reactions: Adverse reactions included diarrhea, flatulence, fatigue, palpitation, nausea and vomiting. The number of patients with adverse reactions was recorded.

Serum inflammatory factor levels

The concentrations of IL-6, TNF-α, and CRP were compared before treatment and 3 months after treatment.

Neurological functional recovery

The patients' neurological function was assessed using scores based on NIHSS. The lower the score, the better the neurological function. The time nodes of comparison were pre-therapy, 3 months post-therapy and 6 months post-therapy [16].

Statistical analysis

The results of this study were processed using SPSS 20.0, while graphs were drawn with GraphPad Prism 7. Enumerated and measured results were compared with χ^2 and *t*-tests, respectively. Values of $p < 0.05$ indicated that the differences were statistically significant.

RESULTS

MMSE score

Table 2 shows that after treatment, the MMSE score was markedly higher in A than in B.

CDR scores

After treatment, the CDR scores of group A were significantly lower than those of group B ($p < 0.05$).

ADL scores

After treatment, the ADL scores in group A were significantly lower than those in group B ($p < 0.001$).

Incidence of adverse reactions

The 2 groups were similar in incidence of unwanted events, and no serious complications such as liver and kidney dysfunction were observed in the patients.

Serum inflammatory factor levels

After treatment, the levels of inflammatory factors were lower in A than in B, as displayed in Table 5.

Table 2: MMSE scores (mean ± SD)

Time	Group A	Group B	*t*	*P*-value
Before treatment	17.21±5.65	17.25±5.68	0.039	0.969
3 months after treatment	19.21±2.12	18.21±2.54	2.341	0.021
6 months after treatment	21.00±2.48	19.20±2.26	4.155	<0.001

Table 3: CDR scores (mean ± SD)

Time	Group A	Group B	*t*	*P*-value
Pre-therapy	2.56±0.56	2.54±0.58	0.192	0.848
3 months post-therapy	1.98±0.44	2.22±0.56	2.610	0.010
6 months post-therapy	1.65±0.42	1.89±0.43	3.093	0.003

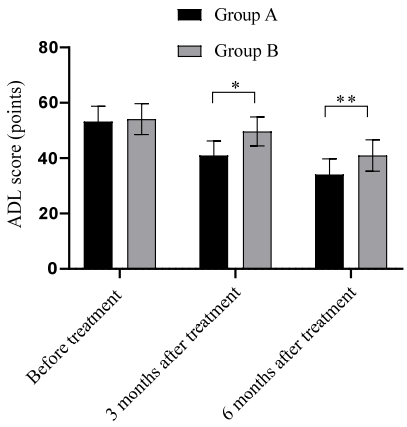

Figure 1: Comparison of ADL scores (mean ± SD). *P < 0.001, ADL score in group A at 3 months after treatment vs the ADL score in group B at 3 months after treatment; ** p < 0.001, the ADL score in group A at 6 months after treatment vs ADL score in group B at 6 months after treatment

Neurological functional recovery

After treatment, the neurological functional recovery in group A was better than that in group B (p < 0.001).

DISCUSSION

Vascular dementia is often caused by stroke and other diseases. The onset of this disease is insidious: the patients do not show obvious dementia symptoms at the early stage. It is only when the disease progresses to irreversible stage that severe decline in neurological function and executive function become manifest. At this time, interventional therapy often has poor effect, and the daily life of the patient has already been significantly negatively affected. Currently, the etiology of vascular dementia is not clear. However, it has been speculated that this disease is closely related to cerebral atherosclerosis. In addition, inflammatory factors block the damaged brain tissue and worsen cerebral blood flow in patients. Therefore, the treatment of such patients should aim at reducing inflammatory factor levels and improving cerebral microcirculation in patients.

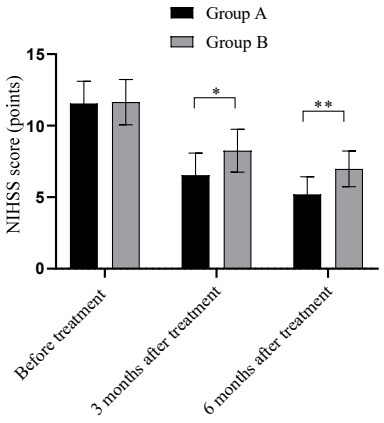

Figure 2: Comparison of NIHSS scores (mean ± SD). * P < 0.001, NIHSS score in group A at 3 months after treatment vs NIHSS score in group B at 3 months after treatment; **p < 0.001, NIHSS score in group A at 6 months after treatment vs NIHSS score in group B at 6 months after treatment

Table 4: Comparison of incidence of adverse reactions {n (%)}

Group	Diarrhea	Flatulence	Fatigue	Palpitation	Nausea and vomiting
A	1(1.7)	2(3.3)	2(3.3)	1(1.7)	3(5.0)
B	2(3.3)	1(1.7)	2(3.3)	1(1.7)	2(3.3)
χ^2	0.342	0.342	<0.001	<0.001	0.209
P-value	0.559	0.559	1.000	1.000	0.648

Table 5: Comparison of serum inflammatory factor levels (mean ± SD, ng/L)

Factor	Group A	Group B	*t*	*P*-value
CRP (mg/L)				
Before treatment	12.56±2.54	12.54±2.57	0.043	0.966
After treatment	5.55±1.11	7.98±1.65	9.465	<0.001
TNF-α (pg/mL)				
Before treatment	310.65±15.98	311.65±15.87	0.344	0.732
After treatment	157.98±15.54	298.65±15.84	49.104	<0.001
IL-6 (ng/L)				
Before treatment	295.65±25.21	296.65±25.98	0.214	0.831
After treatment	230.11±26.98	254.65±25.87	5.085	<0.001

Butylphthalide is a drug frequently used in the clinic for the treatment of Alzheimer's disease. In this study, butylphthalide not only optimized the compensatory ability of cerebral collateral circulation, but it also prevented excessive activation of oxidase and protected the mitochondrial function of the patients. In this study, CDRS score was better in group A patients, suggesting that the cognitive function of patients in group A was improved. This is because donepezil tablets exerted good inhibitory effect on acetylcholinesterase, and butylphthalide soft capsules further weakened apoptosis of neurons and reduced the release of free radicals. The MMSE scores in group A after treatment were higher than those in group B. This also confirmed that the cerebral blood circulation was improved, ischemic cerebral perfusion was better, and the neurotoxins in patients were effectively eliminated. These changes explain why the cognitive function and mental state of patients in group A were better.

Besides cerebral microcirculation, serum inflammatory factors also play crucial roles in the development of vascular dementia. At the onset of this disease, the neurons of patients with vascular dementia release inflammatory factors such as IL-6 and TNF-α, and these pro-inflammatory factors accelerate the release of other inflammatory factors, resulting in the presence of a large number of inflammatory factors in the damaged brain tissue. Then, the damaged blood vessels are blocked again, and the brain hypoxia of patients becomes more severe [17]. In addition, white blood cells can also directly cause brain tissue damage. Therefore, it is essential to reduce the inflammatory factor levels in patients with vascular dementia.

This study showed that the inflammatory factor levels in group A after treatment were lower than those in group B. The reason for this is that butylphthalide soft capsule not only exerts the effect of scavenging free radicals, but it also exerts anti-inflammatory effect, and it inhibits the release of pro-inflammatory factors, thereby reducing hippocampal damage and promoting neurological functional recovery. This explains why the inflammatory factor levels and neurological functional recovery of patients in group A were better than those of group B patients.

This study showed that the CDR and ADL scores were lower in group A patients. This is in agreement with the findings of Holm et al [18]. In the study of Holm *et al*, the vascular dementia subjects were treated with donepezil tablets and butylphthalide soft capsules, while control subjects received donepezil tablets only. At 6 months after treatment, CDR score and ADL score of the experimental group at 6 months after treatment (1.60 ± 0.42 and 34.54 ± 5.61, respectively) were lower than the control group values [18]. This indicates that the combination of donepezil tablets with butylphthalide soft capsules reduced nerve injury in patients, improved cognitive level, and further improved the quality of daily life. In addition, the study found that incidence of unwanted events were similar in the 2 groups, and none of the patients had serious complications such as liver and kidney dysfunction, indicating that the combination of the two drugs was safe, well tolerated by patients, and worthy of clinical application.

CONCLUSION

This study has shown that the combination treatment of vascular dementia patients using donepezil tablets and butylphthalide soft capsules reduces inflammatory factor levels, and improves cognitive level and quality of life, with good neurological functional recovery and low incidence of adverse reactions. Therefore, this treatment strategy is promising for use in actual clinical practice.

DECLARATIONS

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Conflict of interest

No conflict of interest is 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. FM and JX conceived and designed the study, and drafted the manuscript. Fuqiang Ma, Tao Chen, Yanqiu Wang and Junxia Xu collected, analyzed and interpreted the experimental data. TC and JX revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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