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Original Article

Effect of the combination of donepezil with hyperbaric oxygen therapy and functional rehabilitation training on Parkinson's disease dementia and the neurological function system

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Abstract: Objective: To explore the effect of the combination of donepezil with hyperbaric oxygen therapy and functional rehabilitation training in patients with Parkinson's disease dementia (PDD). Methods: We selected 122 PDD patients for the prospectively non-randomized controlled clinical study. Group A (n=60) was treated with donepezil hydrochloride alone, and group B (n=62) was treated with donepezil hydrochloride, hyperbaric oxygen therapy and functional rehabilitation training. Both groups received conventional symptomatic treatment. Unified Parkinson's Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA) scale, Barthel index scale, and 39-item Parkinson's Disease Quality of Life scale (PDQ-39) were used to evaluate therapeutic effect, cognitive function, self-care ability, and quality of life. Serum interleukin-1β (IL-1β) and interleukin-6 (IL-6) concentrations were determined by ELISA. Results: The effective rate of group B was significantly higher than that of group A (P<0.05). After treatment, MoCA score and Barthel index in both groups were significantly increased, with a significantly larger increase in group B (all P<0.05). PDQ-39 scores in both groups were significantly decreased (both P<0.001), with a significantly larger decrease in group B (P<0.01). The serum IL-1β and IL-6 concentrations in both groups were significantly decreased, with a significantly larger decrease in group B (all P<0.001). Conclusion: Combined treatment of donepezil, hyperbaric oxygen and functional rehabilitation training has a certain therapeutic effectiveness in PDD patients and can improve nervous system function and quality of life. Inhibition of serum IL-1β and IL-6 levels may be a therapeutic mechanism.

Keywords: Hyperbaric oxygen therapy, Parkinson's disease dementia, donepezil, neurological function system

Introduction

Parkinson's disease (PD) is mainly manifested by the pathological degenerative loss of dopaminergic neurons in the substantia nigral pars compacta of the midbrain and the presence of Lewy bodies in some of the surviving neurons. Its incidence rate in people over 60 years old exceeds 1%, and the lifetime prevalence in humans is up to 2% [1]. To date, the pathogenesis of PD still remains unknown. It is considered that age, drugs, body constitution, and social living environment may contribute to the unpleasant status quo [2]. PD clinically presents with a series of motor symptoms such as resting tremor, bradykinesia, and postural instability, and non-motor symptoms like sleep disorders and cognitive impairment [3]. Cognitive impairment exists in early-stage PD patients, and PD dementia (PDD) appears in the late stage [4]. Cognitive deficits, emotional disorders and other dysfunctions in PDD patients seriously affect quality of life of the patients, and these dysfunctions are the key factors for disability and life shortening of the patients [5, 6]. Therefore, it has always been an interesting topic in clinical research to explore befitting treatments for PDD.

Varieties of promising therapies for PDD are in development, and certain progress have been made in recent decades, but long-term dopa-

mine replacement therapy and disease progression itself may be related to gradual ineffectiveness of motor function control and occurrence of adverse reactions of the drugs [7]. Cholinesterase inhibitors, such as donepezil hydrochloride, are common therapeutic drugs administrated for patients with Alzheimer's disease, and they can reversibly inhibit the hydrolysis of acetylcholine and improve acetylcholine levels, thus improving cognitive function of the patients [8]. Previous studies have preliminarily confirmed that donepezil hydrochloride has definite therapeutic effects in PDD, but some patients still present with adverse reactions like diarrhea and aggravation of tremor [9, 10]. Hyperbaric oxygenation can increase the oxygen content of brain tissue and improve the anoxic conditions of the brain and its adjacent tissues, and thus indirectly reduce degeneration and necrosis of brain cells [11]. Functional rehabilitation training belongs to a class of non-drug therapy, so no obvious adverse reactions are present [12]. Recent studies have shown that the concentrations of PDD-related inflammatory factors in cerebrospinal fluid and peripheral blood of PDD patients are significantly increased, with microglial activation and neuronal apoptosis; plus, inflammatory cytokines serve an important role in the disease development [13].

Previous studies have shown that donepezil hydrochloride, hyperbaric oxygen therapy and functional rehabilitation training have significant benefits on the recovery of PD patients [14-16]. There are few studies reporting on the combined application of the three treatments in PDD patients. This study adopted this combination treatment and observed the changes of inflammatory factors, IL-1β and IL-6, aiming to provide a reference basis for PDD treatment.

Materials and methods

Patients

We selected 122 PDD patients for the prospectively non-randomized controlled clinical study. Of those patients, 62 receiving combined treatment of donepezil hydrochloride, hyperbaric oxygen therapy and functional rehabilitation training who were taken as group B, and the remaining 60 treated with donepezil hydrochloride alone were taken as group A. In group A, there were 38 males and 22 females, aged from 58 to 79 years old (median: 65.1±5.8 years old), and their disease duration ranged from 2 to 8 years (median: 3.7±1.3 years). In group B, there were 42 males and 20 females, aged from 60 to 81 years old (median: 66.2±6.4 years old), and their disease duration ranged from 1 to 8 years (median: 3.8±1.1 years). The study was approved by the Medical Ethics Committee of Southwest Medical University, and written informed consents were obtained from all the guardians of the patients.

All patients were diagnosed with PDD according with the UK Parkinson's Disease Society Brain Bank diagnostic criteria for PD [17] and the diagnostic criteria for dementia from the Diagnostic and Statistical Manual of Mental Disorders released by the American Psychiatric Association [18]. Their Montreal Cognitive Assessment (MoCA) [19] scores ranged from 13 to 25. Patients with severe cognitive impairment and/or dyskinesia; or who had brain surgery previously; or were complicated with severe liver and/or kidney dysfunction, cerebral blood circulation disorder, connective tissue disorder, endocrine and metabolic disorder, malignant tumor, hematopoietic disorder, autoimmune disease, heart and/or lung dysfunction, Alzheimer's disease, or other neuropsychiatric diseases; or whose MoCA score was less than 10; or who had other psychotropic drug abuse and/or alcoholism; or who were intolerant to the therapeutic drugs and methods in this study were excluded.

Treatments

Both groups received conventional symptomatic treatment, including administration of neuroprotective drugs like aspirin and madopar for the brain. Group A and B were treated with donepezil hydrochloride (Chongqing Zein Pharmaceutical Co., Ltd., China). The patients were orally administrated at a dose of 5 mg/d in the first 4 weeks, and then a dose of 10 mg/d for the subsequent 12 weeks. Additionally, group B was given hyperbaric oxygen therapy and functional rehabilitation training every day while receiving oral administration of donepezil hydrochloride. The medical hyperbaric oxygen chamber (Yantai Hongyuan Oxygen Industry Co., Ltd., China) was pressurized for 25 min, maintained at a pressure of 20 MPa. The patients received stable oxygen inhalation for 85 min via mask with a halftime resting for 15

min, and the chamber was decompressed for 15 min after the halftime resting. The therapy was performed once a day, 5 days per week. Both groups received treatments for 8 weeks.

Functional rehabilitation training included exercise training, memory function training, and attention training. Exercise training focused on muscle tension, walking gait, language function and facial movement, and it was carried out once a day with the assistance of family members and nursing staff. As to memory function training, recitation or first-letter mnemonics was adopted, and external objects were also used to assist memory; each training lasted 30 min. In terms to attention training, an assistant wrote Arabic numerals or English letters in randomized order on a white paper, then the patient used a pen to cross out the numerals or letters designated by the assistant; in order to raise the difficulty, more rows or groups of numerals or letters were added on the white paper; each exercise was limited to 15 min. The therapeutic effect was evaluated after 3 months of the aforementioned trainings.

Outcome measures

The therapeutic effect of the patients was evaluated according to the Unified Parkinson's Disease Rating Scale (UPDRS) [20]. The scale involved six items including mentation, behavior, mood, activities of daily living, motor examination, and complications of therapy. Each item had 5 grades (0-4 points), with 0 indicating normality and 4 the most sever of the symptoms. The patients that could take care of themselves with obvious improvement in muscular tension and motor function were thought to be markedly effective. The patients that could take care of themselves with the help of others with certain improvement in muscular tension and motor function were thought to be effective. If the clinical symptoms and signs of the patients were not improved or even aggravated compared with those before treatment it was thought to be not effective. (Markedly effective cases + Effective cases)/Total cases in group * 100% = Effective rate.

Montreal Cognitive Assessment (MoCA) scale was used to evaluate the cognitive function before and after treatment, including 8 cognitive dimensions, memory, language, abstract thinking, visuo-spatial abilities, orientation, executive functioning, attention, and concentration, with a total score of 30 points. The higher the score, the better the cognitive function. Barthel index [21] was used to evaluate the self-care ability before and after treatment, including 10 items, feeding, moving from wheelchair to bed/return, personal hygiene, toilet use, bathing, walking on level surface, ascend/descend stairs, dressing, control of the bowels, and controlling bladder, with a total score of 100 points. The higher the score, the stronger the self-care ability. The 39-item Parkinson's Disease Quality of Life scale (PDQ-39) [22] was used to assess the quality of life before and after treatment, including 8 dimensions, activities of daily living, attention & working memory, cognition, communication, depression, functional mobility, quality of life, social relationships, and social support, with a total score of 100 points. The higher the score, the lower the quality of life.

Determination of serum IL-1β and IL-6 concentrations

Serum interleukin-1β (IL-1β) and interleukin-6 (IL-6) concentrations before and after treatment were determined by enzyme-linked immunosorbent assay (ELISA), and the tests were carried out according to the instructions of ELISA kits for IL-1β (Shanghai Guduo Biotechnology Co., Ltd., China) and IL-6 (Tecan (Shanghai) Trading Co., Ltd., China). The absorbance (Optical density value) of each well was measured in sequence at a wavelength of 450 nm using SpectraMax iD multi-function micro-plate reader (Molecular Devices (Shanghai) Co., Ltd.) to determine IL-1β and IL-6 concentrations.

Statistical analysis

The data were analyzed using the SPSS software version 21.0 (IBM Corp, Armonk, NY, USA). Enumeration data were expressed as the number of cases/percentage (n/%). Between-group comparison of enumeration data was conducted by chi-square test. Measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Between-group comparison of measurement data was conducted by independent-samples t-test. Within-group comparison was conducted using the paired t-test. For all analyses, $P<0.05$ was considered statistically significant.

Table 1. General data ($\bar{x}$ ± sd)

	Group A (n=60)	Group B (n=62)	t/χ^2	P
Sex (male/female)	38/22	42/20	0.262	0.608
Age (year)	65.1±5.8	66.2±6.4	0.994	0.322
Body mass index (kg/m^2)	22.69±2.01	22.47±1.96	0.612	0.542
Disease duration (year)	3.7±1.3	3.8±1.1	0.459	0.647
Education time (year)	10.6±3.9	10.4±3.5	0.298	0.766
Hypertension (yes/no)	5/55	5/57	0.003	0.957
Diabetes mellitus (yes/no)	3/57	2/60	0.244	0.621
Smoking history (yes/no)	30/30	35/27	0.510	0.475
Drinking history (yes/no)	29/31	32/30	0.131	0.717
Place of residence (urban/rural)	41/19	47/15	0.847	0.357
Tremor (yes/no)	16/44	13/49	0.546	0.460
Hallucinations (yes/no)	15/45	17/45	0.092	0.761
Depression (yes/no)	47/13	44/18	0.873	0.350
Falls/gait abnormalities (yes/no)	25/35	29/33	0.322	0.570

Table 2. Comparison of therapeutic effect (n, %)

	Marked effectiveness	Effectiveness	Non-effectiveness	Effective rate
Group A (n=60)	21 (35.00)	24 (40.00)	15 (25.00)	45 (75.00)
Group B (n=62)	31 (50.00)	24 (38.71)	7 (11.29)	55 (88.71)
χ^2				3.877
P				0.049

Results

General data

There were no significant differences between the two groups in sex, age, body mass index, disease duration, education time, hypertension, diabetes, smoking history, drinking history, place of residence, tremor, hallucinations, depression, falls/gait abnormalities (all P>0.05; **Table 1**).

Comparison of therapeutic effect

The effective rate in group A was 75.00%, and that in group B was 88.71%. The effective rate of group B was significantly higher than that of group A (P<0.05; **Table 2**).

Comparisons of MoCA score and Barthel index before and after treatment between the two groups

There were no significant differences in MoCA score and Barthel index between the two groups before treatment (both P>0.05). After treatment, MoCA score and Barthel index score in both groups were significantly increased (both P<0.05); compared with group A, group B presented with significant higher increases on MoCA score and Barthel index score (both P<0.05). See **Table 3**; **Figure 1**.

Comparisons of PDQ-39 score before and after treatment between the two groups

There was no significant difference in PDQ-39 score between the two groups before treatment (P>0.05). PDQ-39 scores in both groups after treatment were significantly decreased (both P<0.001), while the decrease of PDQ-39 score in group B was significantly lower than that in group A (P<0.01). See **Figure 2**.

Comparisons of serum IL-1β and IL-6 concentrations before and after treatment between the two groups

There were no significant differences in serum IL-1β and IL-6 concentrations between the two groups before treatment (both P>0.05). The concentrations of serum IL-1β and IL-6 in both groups were significantly reduced (both P< 0.001), and the concentrations of serum IL-1β and IL-6 after treatment in group B were significantly lower than those in group A (both P<0.001). See **Table 4**; **Figure 3**.

Discussion

PDD is a common clinical symptom of the elderly, and mainly manifestes as central nervous system lesions [23]. Most PD initially appears in a latent mode, and PD patients will suffer from bradykinesia, resting tremor, hypermyotonia and cognitive dysfunction as with a slow progression, which can seriously affect quality of life of the patients [24, 25].

Table 3. Comparison of MoCA score and Barthel index before and after treatment ($\bar{x} \pm sd$)

	MoCA score		t	P	Barthel index		T	P
	Before treatment	After treatment			Before treatment	After treatment		
Group A	17.67±4.31	19.43±4.01	2.316	0.022	36.72±6.96	53.59±15.59	7.654	<0.001
Group B	17.32±3.59	20.82±3.28	5.667	<0.001	36.09±7.23	78.85±18.63	16.850	<0.001
t	0.488	2.099			0.490	8.108		
P	0.626	0.038			0.625	<0.001		

Note: MoCA: montreal cognitive assessment.

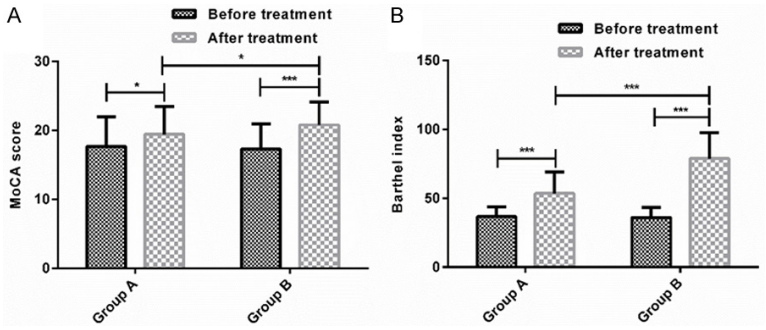

Figure 1. Comparison of MoCA score (A) and Barthel index (B) before and after treatment. Compared with the same group before treatment, *P<0.05, ***P<0.001; compared with the group A after treatment, *P<0.05. MoCA: Montreal Cognitive Assessment.

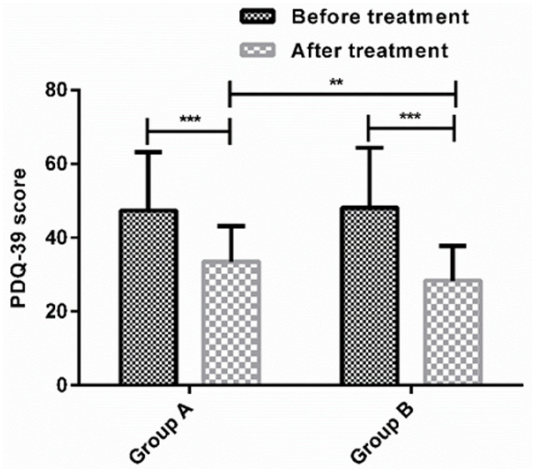

Figure 2. Comparison of PDQ-39 score before and after treatment. Compared with the group A after treatment, **P<0.01; compared with the same group before treatment, ***P<0.001. PDQ-39: 39-item Parkinson's Disease Quality of Life scale.

Currently, there is no clear interpretation on the pathogenesis of PDD. Some scholars hold the idea that its onset is closely related to the decrease of dopaminergic neurons and the damage of ascending cholinergic pathway [26]. Donepezil hydrochloride belongs to specific cholinesterase inhibitors and can prevent hydrolysis of acetylcholine receptor and increase acetylcholine level in the synaptic cleft, thus treating PDD [27]. As to the administration of donepezil for PDD, Dubois et al. found that donepezil could improve the cognition, executive function and global status in PDD, but it was prone to adverse events present in mostly moderate severity [28]. In the study by Sawada et al., donepezil provided beneficial effects on score changes of Parkinson's Psychiatric Questionnaire, Mini-Mental State Examination, and Wechsler Memory Scale for PD patients within 2 years, but it had no prophylactic effect on development of psychosis in PD [29]. Although donepezil has significant benefits for PDD treatment, the effect of drug therapy alone is not satisfactory at present [30]. Hyperbaric oxygen can increase oxygen content in the blood, enhance oxygen diffusing capacity between the lungs and the blood, and further improve systemic hypoxia, which has a good clinical effect on hypoxia and ischemic diseases [31]. Previous studies have shown that functional rehabilitation training can enhance patients' neurological activities related to visuo-spatial abilities, orientation ability, and problem-solving ability [32]. There have been few studies on the combined application of donepezil, hyperbaric oxygen therapy and rehabilitation training for PDD.

In this study, we found that the combined treatment of donepezil, hyperbaric oxygen therapy and rehabilitation training has definite clinical effects on PDD patients, and it can significantly improve the nervous system function and qual-

Table 4. Comparison of serum IL-1β and IL-6 concentrations before and after treatment ($\overline{x} \pm sd$)

	IL-1β (ng/L)		t	P	IL-6 (μg/L)		T	P
	Before treatment	After treatment			Before treatment	After treatment		
Group A	58.37±5.69	41.27±5.39	16.900	<0.001	221.56±32.86	189.56±18.56	6.568	<0.001
Group B	59.42±5.46	34.36±5.51	25.440	<0.001	227.49±33.68	154.69±20.26	14.580	<0.001
t	1.040	7.000			0.984	9.903		
P	0.300	<0.001			0.327	<0.001		

Note: IL-1β: interleukin-1β; IL-6: interleukin-6.

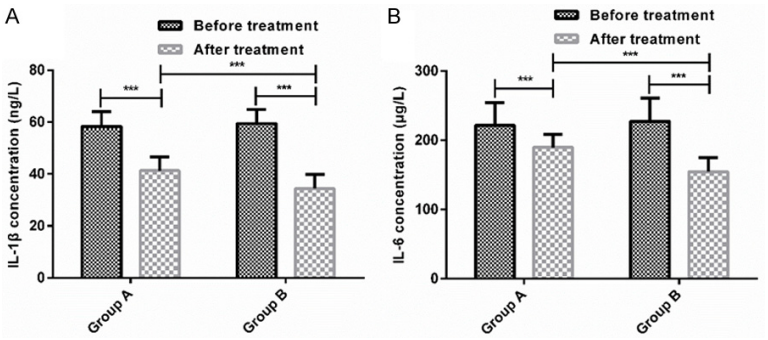

Figure 3. Comparison of serum IL-1β (A) and IL-6 (B) concentration before and after treatment. Compared with the same group before treatment, ***P<0.001; compared with the group A after treatment, ***P<0.001. IL-1β: interleukin-1β; IL-6: interleukin-6.

ity of life. Pan et al. found that hyperbaric oxygen combined with madopar has a protective effect on dopaminergic neurons in substantia nigra of rats with 6-hydroxydopamine-induced PD, which can reduce oxidative stress and protect against Bax/Bcl-2-mediated apoptosis [33]. Reuter et al. concluded that multimodal cognitive rehabilitation program including cognitive training and endurance training can promote the scores of Alzheimer's disease Assessment Scale cognitive subscale and of the Scales for Outcomes in Parkinson's disease-Cognition [34]. These findings are similar to our research. These changes may be account for the improvement on dysfunctions in balance, muscle strength, gait and cognitive function [35]. Under administration of drugs for PDD, hyperbaric oxygen therapy can protect neurons and reduce brain injury and appropriate functional rehabilitation training can maximize the recovery of neurological function, thus improving clinical efficacy, which may be responsible to those similar findings.

A study showed that PD patients showed signs of peripheral and central inflammation, including elevated cytokines in serum and cerebrospinal fluid, and presence of activated microglia [36]. IL-6, a key role in the central nervous system, can stimulate the differentiation of astrocytes, primary dorsal root ganglion neurons and hippocampal neurons, and it may also present with neurotoxicity related to poor prognosis of neural development [37]. Blum-Degena et al. found that IL-1β and IL-6 concentrations are elevated in cerebrospinal fluid of patients with sporadic Alzheimer's disease or de novo PD [38]. Some researchers reported that the concentrations of serum cytokines including IL-6, tumor necrosis factor-2 receptor, and soluble interleukin-2 receptor in PD patients were increased as compared with the control group [39]. Therefore, inhibition of serum inflammatory factors may be one of the therapeutic mechanisms for PDD patients. In this study, our results indicate that the combination of donepezil hydrochloride with application of hyperbaric oxygen therapy and functional rehabilitation training can improve the inflammatory response of PDD patients. Hwang et al. found that donepezil could significantly inhibit the inflammatory reaction of patients with Alzheimer's disease, suppressed the production of nitric oxide and tumor necrosis factor-α in microglia, and inhibited the gene expression of inducible nitric oxide synthase, IL-1β and tumor necrosis factor-α [40]. Matchett et al. reported that hyperbaric oxygen therapy was helpful to improvement on brain oxygenation and reductions in blood-brain barrier damage, inflammation, cerebral edema, intracranial pressure, oxidation stress, metabolic disorder, apoptosis and cell death, as well as promotion of nerve regeneration [41]. Synergistic effects of the combined treatment of donepezil, hyperbaric oxygen therapy and functional rehabilitation

training may account for the improvement on PDD. Inhibiting the concentration of inflammatory factors may be one of the therapeutic mechanisms.

However, there are still some deficiencies in the study. This study is a prospective non-randomized controlled clinical study. Non-randomization may produce imbalances in patient characteristics. The risk factors of PDD patients are not put into observation. Moreover, the specific regulatory mechanisms of IL-1β and IL-6 in PDD are not thoroughly studied here. These deficiencies need to be put into consideration in future research to further support the results of this study.

Combined treatment of donepezil, hyperbaric oxygen and functional rehabilitation training had certain effectiveness in PDD patients and can improve the nervous system function and quality of life of the patients. Inhibition of the concentration of serum IL-1β and IL-6 may be a therapeutic mechanism.

Disclosure of conflict of interest

None.

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