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Original Article

The effects of modified wuhu zhuifeng san on the motor symptoms and serum IL-1β, Cys-C, and Hcy levels in elderly Parkinson's disease patients

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Abstract: Objective: This study was designed to investigate the effects of modified wuhu zhuifeng san on elderly Parkinson's disease patients in terms of their motor symptoms and serum interleukin-6 (IL-1β), cystatin-C (Cys-C) and homocysteine (Hcy) levels. Methods: 77 elderly patients with Parkinson's disease admitted to our hospital from February 2015 to August 2017 were divided into two groups according to the treatment methods they received. The patients in the control group (the CG, n=38) were given levodopa and benserazide tablets only, but those in the observation group (the OG, n=39) were managed with modified wuhu zhuifeng san in addition to levodopa and benserazide tablets as given in the CG. Before and after the treatment, these patients' TCM symptom scores, their clinical efficacy, their unified Parkinson's disease rating scale (UPDRS) scores, their serum IL-1β, Cys-C, and Hcy levels, and their Parkinson's disease questionnaire-39 (PDQ-39) scores were recorded. Results: (1) The OG showed lower TCM symptom scores than the CG (P<0.05). (2) The total efficiency was 94.87% in the OG (37/39), higher than the rate of 68.42% (28/38) in the CG (P<0.05). (3) The UPDRS II, UPDRS III, and UPDRS TV scores in the OG were lower than they were in the CG (P<0.05). (4) After the treatment, the IL-1β, Cys-C and Hcy levels in the CG were higher than they were in the OG (P<0.05). (5) Compared with the CG, the OG's PDQ-39 scores were significantly decreased after the treatment (P<0.05). Conclusion: Modified wuhu zhuifeng san is beneficial to elderly Parkinson's disease patients as it improves their motor symptoms, their IL-1β, Cys-C and Hcy serum levels, and their quality of life.

Keywords: Modified wuhu zhuifeng san, elderly patients, Parkinson's disease, motor symptoms, IL-1β, Cys-C, Hcy

Introduction

Parkinson's disease is a common clinical neurological disease, mainly manifested as non-motor symptoms, including autonomic neurological dysfunction, cognitive disorders, and psychologic dysfunction, and motor symptoms, including abnormal posture & gait, static tremor, myotonia, and bradykinesia [1, 2].

The pathogenesis of Parkinson's disease has not been fully found, but it is generally believed that oxidative stress, aging, and environmental and genetic factors play important roles in the occurrence of the degeneration and death of dopaminergic neurons that occur in Parkinson's disease [3, 4]. Parkinson's disease begins insidiously and develops slowly. The initial symptoms are often clumsiness or tremor of hemilimb movement that always affects the contralateral side [5]. A variety of drugs are used for the treatment including catechol-O-methyltransferase inhibitors, compound levodopa, DR agonists, monoamine oxidase B, amantadine, anticholinergic drugs, *etc*., among which levodopa and benserazide hydrochloride are two of the commonly used drugs [6]. However, using drugs to treat Parkinson's disease reduces the efficacy in the cases of long-term application

and increases the incidence of adverse reactions with an increase in the dosage [7]. In recent years, traditional Chinese medicine (TCM) has been found to have unique advantages in the treatment of Parkinson's disease. Many Chinese medicine studies have shown that Chinese medicine has multiple actions in immunoregulation, mitochondrial function, and antioxidant stress [8].

Considering the unique advantages of TCM, this study was designed to combine levodopa and benserazide hydrochloride with TCM, modified wuhu zhuifeng san, so as to achieve the ideal therapeutic effect in elderly patients with Parkinson's disease.

Material and methods

Material

77 elderly patients with Parkinson's disease admitted to our hospital from February 2015 to August 2017 were recruited as a study cohort for a retrospective analysis and divided into two groups according to the treatment methods they received. The patients in the CG (n=38; 20 males and 18 females) were only given levodopa and benserazide tablets, while those in the OG (n=39, 22 males and 17 females) were given modified wuhu zhuifeng san combined with levodopa and benserazide tablets as given in the CG. (1) Inclusion criteria: patients who provided the signed informed consent, patients who met the diagnostic criteria for Parkinson's disease in *Diagnostic Criteria for Parkinson's Disease* [9], and patients who had a course of disease ≤20 years could be enrolled. This study was approved by the Ethics Committee of our hospital. (2) Exclusion criteria: patients who had deficient clinical data, patients who were unlikely to strictly follow the doctor's instructions, patients who had severe underlying diseases that may affect the efficacy evaluation, or patients or who were allergic to the drugs used in this research.

Methods

CG: the patients were given levodopa and benserazide hydrochloride tablets (manufacturer: Shanghai Roche Pharmaceuticals Ltd. SFDA Approval no. H10930198 Specification: 250 mg, 50 mg) orally, 125 mg given 2-4 times daily for 12 weeks.

OG: the patients were given levodopa and benserazide hydrochloride tablets just the same as the patient in the CG, in addition, modified wuhu zhuifeng san, which is composed of 6 g of rhizoma arisaematis, 6 g of periostracum cicada, 12 g of *Gastrodia elata*, 3 g of scorpio, 10 g of bombyx batryticatus, 15 g of rhizome of *Curculigo capitulata*; all the drugs are made into condensed granules and administered with warm water in a divided dosage in the morning and evening daily for 12 weeks.

Observed indicators

TCM symptom score: the primary symptoms include a stiff nape, limb spasms, less movement, limb head tremors; and scored as follows: 0 if asymptomatic, 2 if mild, 4 if moderate, and 6 if severe. The secondary symptoms include a reduced ability to take care of oneself in daily life, hypophrenia or mental disturbances, salivation, seborrhea, upper limb incoordination, slurred speech, head and chest anteversion, and dull facial expressions, and scored as follows: 0 if asymptomatic, 1 if mild, 2 if moderate, and 3 if severe. Before and after the treatment, the sum of these scores above was recorded as the total TCM symptom score [10]. Efficacy index = (TCM symptom score before treatment - TCM symptom score after treatment)/TCM symptom score before treatment ×100%.

Clinical efficacy: the evaluation of the clinical efficacy was based on the efficacy indices, of which ≥90%, 70%-89%, 30%-69%, or ≤29% was separately used as a clinical control, markedly effective, effective, and ineffective. Total effective = clinical control + markedly effective + effective [11].

Unified Parkinson's Disease Rating Scale (UPDRS): before and after treatment, the UPDRS II (daily activities), UPDRS III (motor function) and UPDRS TV (motor complications) were used to evaluate the patients' motor symptoms and complications. The motor symptoms were directly proportional to the score [12]. Cronbach's α coefficient is 0.858.

Biochemical indicators: before and after the treatment, 2 ml of fasting venous blood was collected from the two groups of patients in the early morning and centrifuged at 3000 r/min to separate the serum. The serum IL-1β, Cys-C,

Table 1. The general Information of both groups [n (%)]/($\bar{x}$ ± s)

Items		OG (n=39)	CG (n=38)	t/X^2	*P*
Sex (cases)	Male	22 (56.41)	20 (52.63)	0.111	0.739
	Female	17 (34.69)	18 (47.37)		
Age (years)		68.98±1.28	68.92±1.25	0.208	0.836
Course of the disease (years)		4.16±0.22	4.19±0.25	0.559	0.578
Modified Hoehn & Yahr Evaluation (cases)					
Grade 1		12 (30.77)	11 (28.95)	0.015	0.998
Grade 2		10 (25.64)	10 (26.31)		
Grade 3		10 (25.64)	9 (23.68)		
Grade 4		7 (17.95)	8 (21.05)		

Table 2. TCM syndrome scores in both groups ($\bar{x}$ ± s, points)

Group	Before treatment	After treatment
CG (n=38)	30.62±3.52	22.39±2.28#
OG (n=39)	30.69±3.49	18.02±1.08#,*
t	0.088	10.793
P	0.930	0.000

Note: #indicates *P*<0.05 compared with the value before the treatment; *indicates *P*<0.05 compared with CG.

and Hcy were measured using an enzyme linked immunosorbent assay following the instructions of kits supplied by Hebei Changtian Pharmaceutical Co., Ltd.

Quality of life: the quality of life of the patients in both groups was evaluated before and after the treatment using Parkinson's disease questionnaire-39 (PDQ-39), which is a life quality questionnaire for Parkinson's disease patients composed of 39 parameters covering almost all aspects, including stigma, emotions, activities of daily living, and mobility. Each item is scored on a 0-4 scale: 0 if asymptomatic, 4 if always affected. The score is inversely proportional to one's quality of life [13]. Cronbach's α coefficient is 0.889.

Statistical analysis

SPSS 22.0 was used for the statistical analysis. The measurement data were expressed as the mean ± standard deviation. Independent-sample T tests were used for the normally distributed data, and Mann-Whitney U tests for the data with a non-normal distribution; Paired t tests were used for the intra-group comparisons. The enumeration data were expressed as [n (%)]. X^2 tests were used for the inter-group comparisons. *P*<0.05 indicated statistical significance.

Results

Comparison of the general information

The patients in OG included 22 males (56.41%) and 17 females (34.69%), ranging in age from 61-80 years old (68.98±1.28 on average) and with a disease course of 1-7 years (4.16±0.22 in average); of which the numbers of cases rated 1, 2, 3, or 4 in the modified Hoehn & Yahr system were 12 (30.77%), 10 (25.64%), 10 (25.64%), and 7 (17.95%) respectively. The patients in the CG included 20 males (52.63%) and 18 females (52.63%), ranging in age from 60-79 years old (68.92±1.25 on average)and a with a disease course of 2-8 years (4.19±0.25 on average); of which the number of cases rated 1, 2, 3, or 4 in the modified Hoehn & Yahr system were 11 (28.95%), 10 (26.31%), 9 (23.68%), and 8 (21.05%) respectively. There were no statistically significant differences between the OG and the CG in terms of gender, age, disease course, or modified Hoehn & Yahr evaluation (*P*>0.05) (**Table 1**).

Comparison of the TCM symptom scores in both groups

There was no significant difference in the TCM symptom scores in both groups before the treatment (*P*>0.05). Compared with the scores before the treatment, the TCM symptom scores were reduced in both groups (*P*<0.05), and the scores in the OG were lower than those in the CG (*P*<0.05) (**Table 2**).

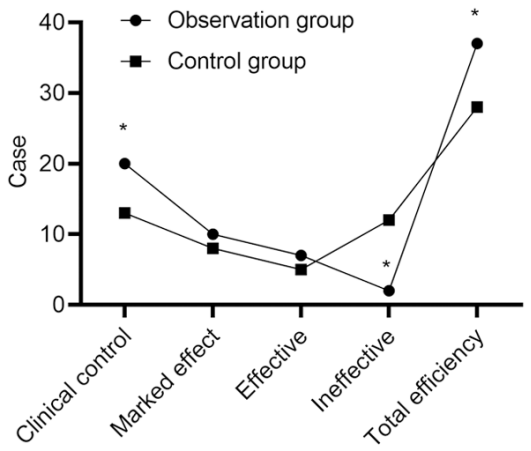

Figure 1. Comparison of the clinical efficacy in both groups. 20 cases were evaluated as the clinical control in the OG, as compared with 13 cases in the CG, $P<0.05$; the number of cases determined to be markedly effective or effective in the OG was 10, and 7 separately, as compared with 8 and 5 in the CG, $P>0.05$; the number of cases determined to be ineffective in the OG was 2, less than the 12 in the CG, $P<0.05$; the total efficiency in the OG was 94.87%, superior to the 68.42% in the CG, $P<0.05$. * indicates $P<0.05$, compared with that in CG.

Comparison of the clinical efficacy in both groups

After treatment, there were 20 cases of clinical control, 10 cases of markedly effective, 7 cases of effective, and 2 cases of ineffective in the OG, for a total efficiency rate of 94.87% (37/39), while the cases in the CG were recorded as 13, 8, 5, and 12, respectively, for a total efficiency rate of 68.42% (28/38) ($P<0.05$) (**Figure 1**).

Comparison of the UPDRS scores in both groups

No significant difference was observed in the two groups with respect to their UPDRS II, UPDRS III, and UPDRS TV scores before the treatment ($P>0.05$). Compared with their scores before the treatment, both groups had reduced UPDRS II, UPDRS III, and UPDRS TV scores after the treatment ($P<0.05$) and the scores in OG were lower than they in the CG ($P<0.05$) (**Table 3**).

Comparison of the biochemical indicators in both groups

Before treatment, the IL-1β level was (14.98±2.52) pg/ml in the OG and (15.02±2.49) pg/ml in the CG, indicating no statistically significant difference ($P>0.05$). After the treatment, the IL-1β level was (10.02±1.28) pg/ml in the OG, which was lower than the level of (12.18±1.98) pg/ml in the CG ($P<0.05$) (**Figure 2**).

Similarly, before the treatment the Cys-C level was (1.29±0.05) mg/L in the OG and (1.31±0.03) mg/L in the CG, showing no statistically significant difference ($P>0.05$), but after the treatment, the Cys-C level was (1.06±0.02) mg/L in the OG, which was lower than the level of (1.25±0.04) mg/L in the CG ($P<0.05$) (**Figure 3**).

Before the treatment, the Hcy level was (18.96±2.23) μmol/L in the OG and (18.99±2.21) μmol/L in the CG, indicating no statistically significant difference ($P>0.05$). After the treatment, the Hcy level was (9.12±1.05) μmol/L in the OG, which was lower than the (15.12±1.03) μmol/L in the CG ($P<0.05$) (**Figure 4**).

Comparison of the PDQ-39 scores in both groups

There was no significant difference in PDQ-39 scores in the two groups before treatment ($P>0.05$). Compared with the scores before the treatment, both groups had reduced PDQ-39 scores after the treatment ($P<0.05$), and the scores in the OG were lower than the scores in the CG ($P<0.05$) (**Table 4**).

Discussion

Parkinson's disease has a high incidence in the clinic, and the elderly are the main victims of the disease. There is not yet a radical treatment with clinical applications [14]. Levodopa and benserazide have been the gold standard in the treatment of Parkinson's disease [15]. Although the drug can effectively alleviate the motor symptoms of patients with Parkinson's disease, it is not ideal for autonomic neurological disorders or non-motor symptoms. At the same time, it may not prevent the progression of the disease and easily causes side effects on the urinary system, on the cardio-cerebrovascular system, on cognition, and on gastrointestinal system, so it is limited in terms of clinical medication [16, 17]. In recent years, it has been found in studies on Chinese medicine that the comparison of TCM and western medicine exerts "effect-enhancing and toxicity-

Table 3. The UPDRS scores in both groups ($\bar{x}$ ± s, points)

Group	UPDRS II		UPDRS III		UPDRS IV	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
CG (n=38)	14.58±2.16	14.58±1.05#	20.56±1.52	18.15±1.02#	2.29±0.52	1.98±0.18#
OG (n=39)	14.60±2.13	10.25±1.03#,*	20.59±1.49	16.02±0.28#,*	2.22±0.51	1.62±0.25#,*
t	0.041	18.267	0.087	12.566	0.596	7.235
P	0.968	0.000	0.931	0.000	0.553	0.000

Note: #indicates *P*<0.05 compared with the value before treatment; *indicates *P*<0.05 compared with the CG.

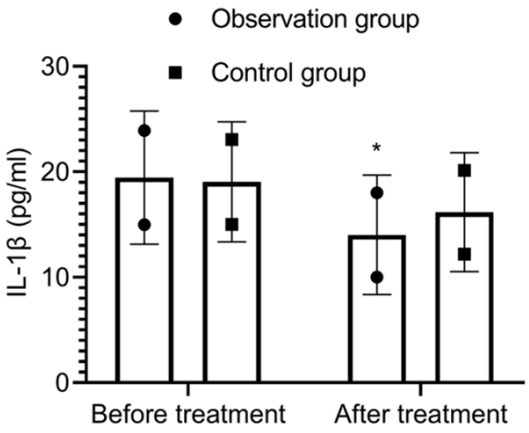

Figure 2. The IL-1β levels before and after the treatment in the two groups. There was no significant difference in the IL-1β levels before the treatment in the two groups (*P*>0.05). After the treatment, the IL-1β in the OG was lower than it was in the CG, *P*<0.05. * indicates *P*<0.05, compared with the level in the CG.

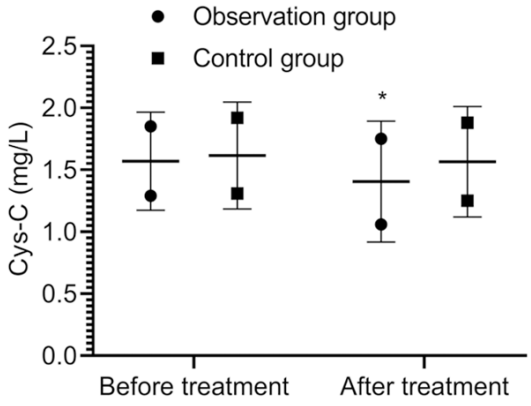

Figure 3. The Cys-C levels before and after the treatment in the two groups. There was no significant difference in the Cys-C levels before the treatment in the two groups, (*P*>0.05). After the treatment, the Cys-C level in the OG was lower than it was in the CG, *P*<0.05. * indicates *P*<0.05, compared with the value in the CG.

reducing" effects, which can further improve the therapeutic outcomes of Parkinson's disease, decrease adverse drug reactions, and postpone the progression of the disease [18].

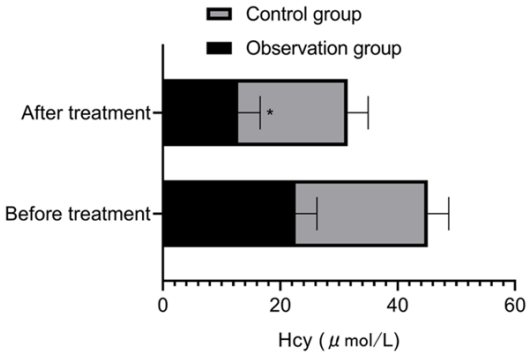

Figure 4. The Hcy levels before and after the treatment in the two groups. There was no significant difference in the Hcy levels before the treatment in the two groups, (*P*>0.05). After the treatment, the Hcy in the OG was lower than it was in the CG, *P*<0.05. * indicates *P*<0.05, as compared with the value in the CG.

Table 4. The PDQ-39 scores in both groups ($\bar{x}$ ± s, points)

Group	Before treatment	After treatment
CG (n=38)	45.89±4.15#	40.12±2.15#
OG (n=39)	45.92±4.12#,*	33.12±1.08#,*
t	0.032	18.123
P	0.975	0.000

Note: #indicates *P*<0.05 compared with the value before the treatment; *indicates *P*<0.05 compared with the CG.

In TCM, Parkinson's disease is classified as "spasmodic syndrome" and "tremor syndrome" caused by the malfunction of the spiritual mechanism and malnutrition in the tendons and vessels [19]. On this basis, the combination of modified wuhu zhuifeng san with levodopa and benserazide hydrochloride tablets showed that the OG had decreased TCM syndrome, UPDRS II, UPDRS III and UPDRS TV, as well as the DQ-39 scores after the treatment compared

with the CG and achieved a superior total efficiency (P<0.05). These results revealed that modified wuhu zhuifeng san may improve the patients' motor symptoms and quality of life. It can be explained by the fact that the rhizome of *Curculigo capitulata* is a sovereign drug that can generate marrow, tonify the kidney and invigorate the circulation of the blood; scorpio can activate the blood circulation; bombyx batryticatus can dissolve phlegm; rhizoma gastrodiae can calm the endogenous wind; rhizoma arisaematis can stop trembling and relieve spasm; and periostracum cicada can expel the wind and relieve convulsions [20].

Studies have shown that patients with Parkinson's disease have a large amount of IL-1β secreted from cholinergic neurons, the cerebrospinal fluid, and the blood [21]. IL-1β plays an important role in the inflammatory response in the local inflammation area. At the same time, it is also closely related to the central nervous system inflammatory response. Patients with Parkinson's disease showed higher levels of IL-1β in cerebrospinal fluid and blood than healthy people. The reduction of IL-1β in such locations suggests improved an neurological function from coloboma [22]. Cys-C is highly expressed in neurological diseases and is a type of cysteine protease inhibitor. When it is noxiously stimulated, the body's Cys-C secretion will increase significantly [23, 24]. Hcy is a sulfur-bearing non-essential amino acid and that induce the generation of superoxide and free radicals to oxidatively damage cells and activate the signaling pathways in apoptosis [25]. Elevated Hcy levels generally promote the progression of Parkinson's disease [26]. In this paper, the serum levels of IL-1β, Cys-C, and Hcy in the OG were lower than the levels in the CG after treatment (P<0.05), indicating the improvement from the modified wuhu zhuifeng san in neurological function and condition of the patients to some extent.

In conclusion, the combination of modified wuhu zhuifeng san with levodopa and benserazide hydrochloride tablets can improve the neurological function, motor symptoms, and quality of life, and postpone the progression of the disease in the treatment of elderly patients with Parkinson's disease.

Although this study has achieved certain results, it also has some limitations. The study included a small cohort, and the results obtained are not sufficiently representative. This requires further expansion of the cohort size in the future.

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Disclosure of conflict of interest

None.

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