Tropical Journal of Pharmaceutical Research July 2023; 22 (7): 1675-1681
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i7.19

Original Research Article

Effect of ginkgo leaf tablets combined with compound carbidopa on patients with Parkinson's disease

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Sent for review: 14 April 2023 *Revised accepted: 21 July 2023*

Abstract

Purpose: *To determine the effect of a combination of ginkgo leaf tablets with compound carbidopa tablets on cognitive function, serum homocysteine (Hcy), malondialdehyde (MDA) and neuron-specific enolase (NSE) levels in patients with Parkinson's disease (PD).*
Methods: *A total of eighty (80) PD patients admitted to The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China between December 2020 and December 2022 were randomly divided into two groups: Western medicine group (n = 40, using compound carbidopa tablets alone) and combination group (n = 40, using ginkgo leaf tablets combined with compound carbidopa tablets), and orally treated for 3 months. Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to assess cognitive function before and after treatment. High-performance liquid chromatography was used to determine serum Hcy levels, while enzyme-linked immunosorbent assay (ELISA) was used to evaluate serum MDA and NSE levels. Adverse reactions were also recorded during treatment.*
Results: *Total response rate following treatment in combination group was significantly higher than in Western medicine group (95.00 vs 80.00 %, $p < 0.05$). After treatment, MMSE and MoCA scores in combination group were significantly higher ($p < 0.05$) than those in Western medicine group, while serum Hcy, MDA and NSE levels in combination group were significantly lower than those in Western medicine group ($p < 0.05$). During treatment, there was no significant difference in incidence of adverse reactions between the two groups ($p > 0.05$).*
Conclusion: *Ginkgo leaf tablets in combination with carbidopa significantly improve cognitive functions associated with PD with high safety, when compared to carbidopa tablets alone. However, further clinical trials are commended to validate these findings.*

Keywords: *Ginkgo leaf tablets, Carbidopa tablet, Parkinson's disease, Cognitive function, Homocysteine, Malondialdehyde, Neuron-specific enolase*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

The pathogenesis of Parkinson's disease (PD) is complex and diverse. It is a neurodegenerative disorder that primarily affects motor system, leading to symptoms such as tremors, stiffness and difficulty with movement and coordination. Parkinson's disease is characterized by loss of

dopamine-producing cells in brain, particularly in a region called substantia nigra. In addition to being related to environmental and genetic factors, oxidative stress and nerve cell apoptosis are also important steps involved in physiological and pathological process of PD [1]. Previous studies have shown [2] that onset of PD is closely related to decrease of striatal dopamine content in the population. Therefore, levodopa, which can supplement dopamine, is a representative drug for treatment of PD. Once levodopa enters central nervous system (CNS), it is converted to dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC). This dopamine then acts on dopamine receptors in brain, compensating for dopamine deficiency in Parkinson's disease. Following oral administration, most of the levodopa is converted into dopamine in the periphery and finally, only 1 % of levodopa enters central nervous system to exert its drug effect. It, therefore, needs to be supplemented by increasing the dose [3-5].

The disadvantage of insufficient central nervous system drug dosage, in spite of excessive oral drug dosage, easily leads to many adverse events and therapeutic effect of long-term use can gradually decline or even cause treatment fluctuations and other complications [5]. Therefore, increasing effective drug dosage in central nervous system is key to treatment. Carbidopa cannot pass through the blood-brain barrier, but it inhibits conversion of peripheral levodopa into dopamine, thereby increasing amount of levodopa in circulation [6]. “Compound carbidopa”, composed of levodopa and carbidopa Pa tablets, effectively increases amount of levodopa entering the central nervous system to achieve original purpose of treating PD. This combination relieves nausea, vomiting and other discomforting symptoms caused by levodopa tablets alone [6-8].

Although Western medicine such as andodopa and carbidopa improves symptoms of PD by increasing the concentration of dopamine in CNS, it is often associated with nausea and vomiting, dyskinesias, and orthostatic hypotension and its long-term use produces adverse effects. Chinese scholars have integrated treatment concept of traditional Chinese medicine into treatment of PD and found that it is effective in improving the therapeutic effect of PD.

Ginkgo biloba is a seed plant and its various parts have rich pharmacological effects. The leaves and seeds of ginkgo tree are utilized for their potential health benefits, including their antioxidant and anti-inflammatory properties [9]. Literature shows that flavonoids and terpene lactones in Ginkgo leaf extract can improve brain energy metabolism, protect brain nerves, promote learning and memory, and treat neurodegenerative diseases [9]. This study aims to determine the effect of *Ginkgo biloba* leaves combined with compound carbidopa tablets on PD by monitoring cognitive function and physiological indicators related to the onset of PD.

METHODS

General patient information and grouping

A total of eighty (80) PD patients admitted to The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China from December 2020 to December 2022 were selected as research subjects. Subjects were equally divided into two groups by random number table method. Western medicine (control) group (n = 40) was treated with compound carbidopa tablets, while combination group (n = 40) was treated with *Ginkgo biloba* leaves combined with compound carbidopa tablets. This study was approved by the Ethics Committee of The Affiliated Hospital of Xuzhou Medical University (approval no. XMU-01821) and all subjects gave informed consent. All procedures were carried out in accordance with the guidelines of Declaration of Helsinki [10].

Inclusion criteria

Patients with the following criteria were included in the study: Meeting diagnostic criteria of PD [11], with muscle stiffness, slow movement, tremor and other symptoms of neuropathy; no organic lesion on imaging; presence of complete clinical data; good liver and kidney function.

Exclusion criteria

Patients who have developed dementia and cannot cooperate with study, patients with co-existing malignant tumors, patients who cannot cooperate due to other mental disorders apart from dementia, and those with a history of PD treatment and allergy to study drugs were excluded from the study.

Treatments

Western medicine group took compound carbidopa tablets (Xilaimei, manufacturer: Jingjing Pharmaceutical Group Co. Ltd, approval number: National Drug Approval H10950085.) orally for 3 months, with an initial dose of 137.5 mg, taken 3 times daily, and then increased by 137.5 mg daily until the maximum dose of 2.2 g was attained.

Combination group orally received compound carbidopa tablets at the same dose used in the Western medicine group, combined with *Ginkgo biloba* leaves at a dose of 2 tablets each time, 3 times daily, orally for 3 months (manufacturer: Yangzijiang Pharmaceutical Group Co. Ltd, approval number: Z20027949).

Evaluation of parameters/indices

Efficacy

After 3 months, Parkinson's Disease Rating Scale [12] (Unified PD Rating Scale, UPDRS) was used to evaluate curative effect of Western medicine and combined groups. Higher values indicate more severe symptoms. If the UPDRS score before and after treatment is reduced by greater than 30 %, it means PD-related symptoms significantly improved. A UPDRS score reduced by 8 to 29 % before and after treatment indicates that PD-related symptoms improved. When the relevant symptoms do not improve but rather worsen, it is termed ineffective.

Cognitive function

Before and after treatment, mini-mental state examination (MMSE) [13] was used to evaluate the intellectual status and cognitive impairment of subjects. The higher the MMSE score, the better the cognitive function. Approximately 30 points are normal while scores less than 27 points are considered to have cognitive impairment. Montreal Cognitive Assessment (MoCA) [14] was used to evaluate the cognitive symptoms of subjects which includes 7 items, with a total score of 30 points. MoCA greater than or equal to 26 is considered normal, while MoCA between 18 and 26 points signifies mild cognitive impairment; scores between 10 and 17 points in MoCA indicate moderate cognitive impairment, while MoCA less than 10 is severe cognitive impairment.

Detection of serum Hcy, MDA and NSE levels

Before and after treatment, fasting venous peripheral blood was collected from all patients. Serum was separated by centrifugation and sent to the hospital's laboratory for testing. Serum homocysteine (Hcy) level was assayed by high-performance liquid chromatography while serum malondialdehyde (MDA) and neuron-specific enolase (NSE) levels were determined using ELISA kits (Roche Company), according to the instructions of the manufacturer.

Adverse reactions

Occurrence of adverse reactions during the treatment was observed and recorded.

Statistical analysis

Statistical software (SPSS 21.0) was used for data analysis in this study. Age and measurement data were expressed as mean ± standard deviation (SD), and *t*-test was used to compare differences between Western medicine group and combination group. Unit of enumeration data is expressed in percentage (%) and χ^2 test was carried out on them. $P < 0.05$ means the difference is statistically significant.

RESULTS

General data of PD patients

There was no significant difference in general data of PD patients between Western medicine and combination groups ($p > 0.05$). The results are presented in Table 1.

Curative effect of PD patients

Total effectiveness after treatment in combination group was 95.0 %, significantly higher than 80.0 % in Western medicine group ($p < 0.05$). The results are shown in Table 2.

Cognitive function of PD patients

After treatment, MMSE and MoCA scores of PD patients in combination group were significantly higher than those in Western medicine group ($p < 0.05$). The results are presented in Figure 1.

Table 1: Comparison of general data of PD patients in Western medicine and combination groups (mean ± SD, n = 40, %))

Group	Gender (female/male)	Age (years)	Disease duration (years)	BMI (kg/m^2)	Years of education (years)
Western medicine group	12/28	68.33±7.52	5.25±1.37	2 3.82±2.91	9.75±2.14
Combination group	10/30	67.92±7.64	5.31±1.40	2 4.01±2.96	9.85±2.19
t / $\chi 2$	0.251	0.242	0.194	0.289	0.207
P-value	0.617	0.810	0.847	0.773	0.837

Table 2: Comparison of curative effect of PD patients in Western medicine and combination groups after treatment (n = 40)

Group	Valid	Efficient	Invalid	Total effectiveness (%)
Western medicine group	10	22	8	32/40 (80.0)
Combination group	24	14	2	38/40 (95.0)
χ^2 value				4.114
P-value				0.043

Table 3: Comparison of serum Hcy, MDA and NSE levels of PD patients in Western medicine and combination groups before and after treatment (n=40)

Group	Hcy (μmol /L)		MDA (nmol/mL)		NSE (μg/mL)	
	Before treatment	After treatment	Before treatment	After Treatment	Before treatment	After treatment
Western medicine group	26.68±2.15	20.88±3.9*	10.16±1.72	8.02±1.31*	14.16±2.21	12.14±1.59*
Combined group	26.27±2.08	17.09±3.7*#	10.29±1.63	7.37±1.24*#	14.29±2.18	10.98±1.43*#
t – value	0.867	4.413	0.347	2.279	0.265	3.43
P-value	0.389	< 0.001	0.730	0.025	0.792	0.001

Note: Compared with same group before treatment, *$p < 0.05$; compared with Western medicine group, #$p < 0.05$

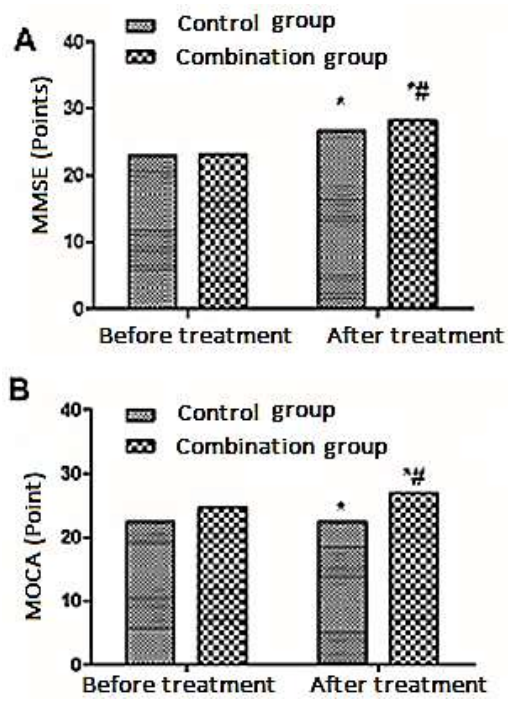

Figure 1: Comparison of cognitive function of PD patients before and after treatment in Western medicine and combination groups. (A) Comparison of MMSE scores before and after treatment of PD patients in Western medicine group and combination group; (B) Comparison of MoCA scores before and after treatment in Western medicine and combination groups. Compared with same group before treatment, *$p < 0.05$; compared with Western medicine group after treatment, #$p < 0.05$

Serum Hcy, MDA and NSE levels

Following treatment, the serum Hcy, MDA, and NSE levels of PD patients in both groups were significantly decreased ($p < 0.05$). Serum Hcy, MDA and NSE levels of the PD patients in combination group were however significantly lower than Western medicine group ($p < 0.05$). The results are seen in Table 3.

Adverse reactions during treatment

During treatment, there was no significant difference in incidence of adverse reactions between groups ($p > 0.05$). Results are shown in Table 4.

DISCUSSION

Parkinson's disease has become the second largest neurodegenerative disease in China, with increasing incidence and the age of onset tending towards the young. The brain metabolism of the elderly is slow and the decrease in dopamine concentration caused by this physiological condition is an important factor causing brain dysfunction [15].

Results of this study showed that total effective rate after treatment in combination group was significantly higher than in Western medicine group.

Levodopa, as a dopamine prodrug, effectively supplements the dopamine missing centrally in central nervous system (CNS) of PD patients. But its availability is limited as most levodopa is lost peripherally, leading to less real availability in central nervous system. Carbidopa, another main component of compound carbidopa, inhibits the peripheral metabolism of levodopa, thus

Table 4: Comparison of adverse reactions during treatment of PD patients in Western medicine and combination groups (n = 40)

Group	Dizziness	Headache	Feel sick and vomiting	Hyperactivity	Incidence of adverse reaction (%)
Western medicine	2	2	4	4	12/40 (30)
Combination	2	1	2	2	7/40 (17.5)
χ2 value					1.726
P-value					0.189

increasing the central levodopa concentration, and as such levodopa exerts its therapeutic effect maximally [16]. Traditional Chinese medicine believes that PD belongs to the category of "flutter" disease in which there is a deficiency in liver and kidney functions, insufficient qi and blood, combined with fatigue, leading to blockage of brain network, which is the main pathogenesis of PD [16].

Ginkgo biloba extracts have the effect of activating blood and dredging meridians, regulating qi and removing blood stasis and promotes the circulation of qi and blood throughout the body, so that it can be unblocked. Thus, symptoms such as numbness of limbs and crooked tongue in patients can be improved [17]. Pharmacological studies have shown that *Ginkgo biloba* extracts have good neuroprotective effects and also accelerate brain metabolism. In addition, *Ginkgo biloba* extracts also have anti-inflammatory and antioxidant effects, thereby alleviating nerve cell apoptosis and promoting cognitive function of PD patients [11-17]. Judging from scores of cognitive function-related scales, MMSE and MoCA in PD patients in combination group were significantly higher than those in Western medicine group, indicating that combined treatment with *Ginkgo biloba* leaves enhanced efficacy of therapy and produced a more significant effect on improving cognitive function of PD patients as well as improving neurological function of patients.

Homocysteine (Hcy) participates in energy metabolism in the body. It promotes generation of oxygen free radicals, brain tissue oxidation and brain cell apoptosis, and it is related to occurrence and development of neurological diseases. The harm of high Hcy levels has been widely recognized. A large amount of Hcy and its derivatives damages dopaminergic neurons in substantia nigra and accelerates progression of PD. Since the level of Hcy is inextricably linked with development of PD, changes in Hcy level also result in changes in PD [18,19].

The results of this study showed that serum Hcy level in combination group was both significantly lower after treatment and significantly lower compared to Western medicine group, indicating that combination treatment is more helpful in improving condition of PD. Occurrence and development of PD involve multiple physiological and pathological processes including inflammatory responses, excessive oxidative stress, abnormal apoptosis of neuritis and mitochondrial dysfunction. As an important product of oxidative stress process, the serum level of malondialdehyde (MDA) indicates degree of oxidative stress in the body [20]. In this study, the serum MDA level of combination group after treatment was significantly lower than that of Western medicine group, indicating that combination treatment improves excessive oxidative stress in PD patients, decreases levels of free radicals in PD patients, and improves antioxidant function in substantia nigra. The oxidative damage in striatum area was reduced, therefore, curative effect was more significant in combination group compared to Western medicine group.

Neuron-specific enolase (NSE) is released into blood in large quantities during brain injury and high serum NSE levels can indirectly indicate brain tissue damage. Although studies have shown that changes in its level are effective markers of cognitive dysfunction in patients with brain injury and PD patients, NSE relationship to secondary cognitive impairment is not clear [21-23]. Results of this study showed that after treatment, serum NSE level of combination group decreased significantly and was also significantly lower than that of patients treated with Western medicine alone, indicating that addition of Ginkgo leaves reduces the degree of neuron damage and promotes the repair of brain damage. Furthermore, there was little difference in in the incidence of adverse reaction between groups of subjects during the treatment period, indicating that combination of drugs will not cause superposition of drug side effects and safety of combination therapy is guaranteed.

Limitations of this study

The number of patients in this study was small and other factors associated with PD were not

considered. Furthermore, the treatment time was short (2 years).

CONCLUSION

Ginkgo biloba leaf tablets combined with compound carbidopa tablets improve cognitive functions of PD and possess high safety and better brain protection compared to carbidopa tablets alone. A more elaborate study involving a larger population would be required to validate the findings of this study.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

Approval for this study was granted by the Ethics Committee of The Affiliated Hospital of Xuzhou Medical University, China (approval no. XMU-01821).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors 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 them.

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