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Research Article

Retrospective Study of Safety and Effectiveness of Levodopa in Patients with Parkinson's Disease

Linghui Wang*, **Lei Xu**

Department of Neurology, Affiliated Hospital of Shandong Medical College, Shandong, China

ABSTRACT

Levodopa has been widely used to treat symptoms of Parkinson's Disease (PD); it is regarded as the most effective therapy for PD at present. Although the usage of levodopa rapidly increased with the number and health burden of PD in China, there is no systematic review to evaluate the efficiency and safety of levodopa in China mainland. Here, we retrospectively analyzed the efficiency and safety of PD treatment using levodopa in Affiliated Hospital of Shandong Medical College during the last decade (2010-2020). A total of 432 patients were included in the present study, with all patients completed at least 24 weeks of levodopa treatment. Unified Parkinson's Disease Rating Scale (UPDRS) and Hamilton Depression Rating Scale (HAMD) were used to evaluate the drug efficacy and management of affective disorder after levodopa treatment, respectively, while any adverse effects of levodopa treatment were recorded. Patients experienced significant improvements in quality of life, as recorded by the mean change from baseline in the UPDRS index ($p<0.001$). A total of Adverse Events (AE) was 432 cases, 2 deaths and 3 serious AE occurred. Wearing off (n=221, 51.15%), dyskinesia (n=174, 40.28%) and constipation (n=131, 30.32%) were the top three AE caused by levodopa. There were no significant differences in adverse events between male and female. In conclusion, our results demonstrated that levodopa treatment offers a promising option for PD patients in the Shandong area. However, more studies with a larger sample are needed to further confirm the efficacy and safety of levodopa treatment in China.

Keywords: Levodopa; Parkinson's disease; Clinical research

INTRODUCTION

Parkinson's Disease (PD) is a slowly progressive parkinsonian syndrome that begins insidiously and is pathologically characterized by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta, the loss of DA content accounts for many of the motor symptoms. Patients with the disease have one or more syndromes including resting tremor, rigidity, slowed movement, decreased dexterity, gait disorder and imbalance. In addition to the progression of the movement disorder after several years, dementia can develop especially in older patients [1-3]. In Chinese populations, common risk factors include rapid eye movement sleep behavior disorder, olfactory dysfunction, and constipation, family history of PD and pesticide exposure [4].

The main treatment for PD is levodopa, which is a precursor to dopamine. Levodopa is clinically used as a dopamine replacement agent for the treatment of PD. It is the most effective medication to improve life quality in patients with idiopathic PD and is typically prescribed to patients whose symptoms become more difficult to control with other medications [5]. Levodopa has been reported effective in slowing PD disease progress [6]. Oral levodopa treatment is always associated with motor complications, such as dyskinesia and "on/off' fluctuations [7]. While other common adverse effects include nausea, dizziness, headache, confusion, psychosis and agitation.

It is said that Chinese PD patients will increase to 4.94 million by 2030, accounting for half of the worldwide PD patients. Although the usage of levodopa rapidly increased with the

Correspondence to: Linghui Wang, Department of Neurology, Affiliated Hospital of Shandong Medical College, Shandong, China, E-mail: walhui@163.com

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number and health burden of PD in China, the clinical study of the efficiency and safety of levodopa in the Chinese population is still insufficient. Thus, the overall objective of this retrospective study was to investigate the efficiency and safety of PD treatment using levodopa in the Chinese population at a local hospital.

MATERIALS AND METHODS

Statement of human rights

This study was approved by the Ethical Committee of the Affiliated Hospital of Shandong Medical College, Shandong and China on June 21, 2020. (No. S2020004, Chairperson Professor Dr. Li Dexiang). Written informed consent was obtained. The study has compiled with the Helsinki declaration.

General and treatment

We collected and analyzed the clinical data of PD patients who were treated with levodopa alone from May 2010 to June 2020 at the Affiliated Hospital of Shandong Medical College. A retrospective review was used to evaluate the efficiency and safety of levodopa. The inclusion criteria were as follows:

1. Slowly progressive disease course.

2. At least two of Tremor, bradykinesia, or postural and gait abnormalities were present.

3. Levodopa naive and oral over 24 weeks.

Patients with prominent oculomotor palsy, cerebellar signs or cognitive abnormality that might not give feedback on the questionnaire were excluded. Patients were taken levodopa capsules (Huanan Pharmaceutical Company, Guangdong and China). The starting dose was 62.5 mg twice a day. Then the amount of administration was progressively increased based on patients' clinical symptoms and drug safety from the second week. The increased dose ranged from 125 to 500 mg per day. Levodopa dose was no further increase until patients reached clinical stabilization. All patients have received at least 24 weeks treatment.

Data collection

The medical records were reviewed and treatment history was extracted. 432 cases were included in this study (271 males and 161 females, 65.23 ± 6.1 years). The patients' demographic information (age, sex and age of diagnosis) and adverse events were recorded.

Assessments

Efficacy: Clinical assessments of patients with PD were recorded by professional physicians before and after the treatment. Levodopa efficacy was assessed by Unified Parkinson's Disease Rating Scale (UPDRS). The primary efficacy outcome measures were changes in UPDRS from baseline to week 60. In addition, depressive symptoms were also recorded and evaluated by Hamilton Depression Rating Scale (HAMD).

Safety: Safety assessments were assessed from reports of any treatment-related adverse events (AEs) after levodopa treatment. AEs were coded using the Chinese Dictionary for Regulatory Activities (C-DRA). The causal relationship is performed using WHO causality assessment criteria. All safety data were assessed by the Affiliated Hospital of Shandong Medical College Safety Monitoring Committee regularly.

Statistical analysis: SPSS software, Ver 19.0 (SPSS, Chicago, IL, USA) was used to conduct statistical analysis. Normally distributed variables were presented as mean ± standard deviation. $\chi 2$ test or Fisher's exact test was used for comparison between different groups. p values were based on a two-sided hypothesis and a $p<0.05$ and $p<0.001$ were considered to indicate statistically significant differences.

RESULTS

Demographic characteristics

The clinical characteristics were as shown in Table 1. A total of 271 males (62.7%) and 161 females (37.3%) participated in this study. The mean age was 65.23 ± 6.1 (range from 42-85) and the mean age when at disease onset was 64.76 ± 9.1. All participants were taking levodopa treatment with an average daily dose of 485.32 ± 343.12 (range: 125-2735 mg/d).

Item	Patients (n=432)
Age (years)	65.23 ± 6.1
Age at disease onset (years)	64.76 ± 9.1
Levodopa dose (mg/day)	485.32 ± 343.12
Male (%)	271 (62.7)

Note: Data are presented as means (± SD) excepted otherwise indicated.

Table 1: The demographic characteristics of PD patients.

Clinical efficacy after levodopa treatment

The efficacy of levodopa treatment was assessed by analysing the mean UPDRS total score. The UPDRS score was classified into four parts, Part I: mentation, behavior and mood, Part II: activities of daily living, Part III: motor examination, Part IV: complications of therapy. We interviewed all participants and analyzed each part of the UPDRS score. Among the total 432 PD patients who participated in the study, the mean UPDRS total score decreased from baseline 34.21 (16.22) to 22.74 (3.89) ($p<0.001$). The mean (SD) UPDRS Part I decreased from 2.92 (1.71) at baseline to 2.01 (0.73) ($p<0.05$). The mean UPDRS Part II score decreased to 3.98 (1.18) from 7.81 (4.34) ($p<0.001$). The mean UPDRS Part III score decreased from 19.15 (10.67) at baseline to 13.04 (4.86) ($p<0.001$), while the mean UPDRS Part IV score decreased from 4.33 (2.63) at baseline to 3.71 (0.65) ($p<0.05$). Finally, the mean PDQ-39 total score decreased from 34.1 (12.6) at baseline to 25.4 (7.4) ($p<0.001$) as in Table 2.

After analysis, the HAMD total score was changed from 22.98 (5.14) at baseline to 15.95 (2.96) ($p<0.001$). In detail, the anxiety/somatization rating reduced 2.11 (1.03) from baseline ($p<0.001$). Weight from 1.49 (0.78) at baseline to 0.93 (0.72) ($p<0.001$). Cognitive disturbance decreased 0.56 (0.77) from 4.13 (0.96). Retardation and sleep disturbance reduced 2.13 (1.23) and 1.01 (0.86) from baseline respectively as in Table 3.

Outcome	Baseline	Change from baseline	p-value*
UPDRS total score	34.21 (16.22)	-11.47 (3.89)	<0.001
Part I: Mentation, Behavior and mood	2.92 (1.71)	-0.91 (0.73)	<0.05
Part II: Activities of daily living	7.81 (4.34)	-3.83 (1.18)	<0.001
Part III: Motor examination	19.15 (10.67)	-6.11 (4.86)	<0.001
Part IV: Complications of therapy	4.33 (2.63)	-0.62 (0.65)	<0.05
PDQ-39 summary index	34.1 (12.6)	-8.7 (7.4)	<0.001

Note: Data are shown as mean (± SD). UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39: 39-item Parkinson's disease questionnaire summary index. *Determined by t-test.

Table 2: Clinical efficacy over time by levodopa treatment.

HAMD item	Baseline	Change from baseline	p-value*
Total score	22.98 (5.14)	-7.03 (2.96)	<0.001
Anxiety/ somatization	6.13 (2.31)	-2.11 (1.03)	<0.001
Weight	1.49 (0.78)	-0.56 (0.72)	<0.001
Cognitive disturbance	4.13 (0.96)	-1.22 (0.77)	<0.001
Retardation	7.92 (2.01)	-2.13 (1.23)	<0.05
Sleep disturbance	3.31 (1.42)	-1.01 (0.86)	<0.001

Note: Data are shown as mean (± SD). HAMD: Hamilton Depression Rating Scale; Anxiety/somatization: HAMD 10, 11, 12, 13, 15, 17; Weight: HAMD 16; Cognitive disturbance: HAMD 2, 3, 9; Retardation: HAMD 1, 7, 8, 14; Sleep disturbance: HAMD 4, 5, 6. *Determined by t-test.

Table 3: HAMD scores at baseline and changes after levodopa treatment.

Besides UPDRS total score, we also analyzed HAMD scores that evaluate the management of affective disorder after levodopa treatment.

HAMD score was also divided into several elements, such as anxiety/somatization, weight, cognitive disturbance, retardation and sleep disturbance.

Adverse effects

Next, we analyzed the adverse events after levodopa treatment. The measurement included both common and severe adverse events such as constipation, weight loss, nausea, delirium, exanthema, as well as levodopa-induced death. All patients who participated had experienced at least one kind of adverse effect. Levodopa treatment resulted in two death cases in the current study. Despite death cases, common side effects such as dyskinesia, constipation have been observed.

More than half of the participated patients experienced the wearing-off phenomenon. Around 40% of patients experienced dyskinesia and 30% of patients experienced constipation, 27.08% of patients lost their weight. Forty-three patients had been reported experiencing impulse control disorder (ICD); and the number of patients who experienced other adverse events such as nausea, delirium, exanthema was 82 (18.98%), 37 (8.56%) and 17 (3.94%) respectively as in Table 4.

Item	Patients, n (%)
Total AE	432 (100)
Any serious AE	3 (0.69)
Discontinuation caused by AE	0 (0)
Death	2 (0.46)
AEs occurring in ≥ 2%	
Wearing off	221 (51.15)
Dyskinesia	174 (40.28)
Constipation	131 (30.32)
Weight decreased	117 (27.08)
Nausea	82 (18.98)
ICDs	43 (9.95)
Delirium	37 (8.56)
Exanthema	17 (3.94)

Note: AE: Adverse Event; ICDs: Impulse Control Disorders.

Table 4: HAMD scores at baseline and changes after levodopa treatment.

DISCUSSION

In this retrospective study, we analyzed 10-year clinical outcomes and adverse events of 432 PD patients that were undergoing levodopa treatment. PD is a neurodegenerative disorder that patients will experience a range of motor and nonmotor symptoms during the course of disease, which largely affects patients' mental health and quality of daily life [8]. We used UPDRS score to assess the changes in motor and nonmotor experiences of daily living and disease complications in PD patients after long-term levodopa treatment. We confirmed that the use of levodopa improves UPDRS scores in all four parts, including improvement in mentation, daily living, motor and complications during therapy. One report that was carried in the USA also showed that levodopa improves both motor and activities of daily living even in patients with long disease duration [9].

Dysfunction in the prefrontal lobe can directly interfere with the functional connectively of default networks in depression, which results in relevant clinical symptoms [10,11]. Therefore, functional abnormalities in the prefrontal lobe can be associated with multiple symptoms in patients with depression [12]. In our study, patients' clinical symptoms were divided into five factors and quantitatively evaluated according to the HAMD. According to our results, levodopa treatment has significantly decreased HAMD score, indicating that long-term levodopa therapy significantly reduced the depression symptoms, which has also been reported in the previous reports [13].

One research has reported that increased mortality in levodopa-treated PD patients relative to age-, race- and gender-matched controls in the U.S. population, which they interpreted as although levodopa treatment effectively treating the motor symptoms and improving life expectancy, it does not normalize life expectancy [14]. As PD progresses, levodopa-resistant motor symptoms and nonmotor symptoms may become more prevalent and may contribute to increased morbidity and mortality [15]. Several patients in our study likely suffered levodopa-resistant motor and nonmotor symptoms that likely contributed to their death.

The wearing-off phenomenon and dyskinesia are the two most common side effects in levodopa treatment especially in long-term, high dose levodopa administration, both have been observed in our study. In advanced PD patients suffering such wearing-off phenomenon and dyskinesia might be improved by treatment of levodopa-carbidopa intestinal gel [16]. While another levodopa-induced complication, ICDs, was reported as well in our study. Another report has found an association between the use of levodopa and ICDs behaviours to have a dose-dependent relationship in Chinese patients. While the frequency of ICDs behaviours is lower than non-Chinese populations (3.53% to 6.3%-14%) [17-20]. Potential risk factors for ICDs such as younger age, male sex, earlier age of disease onset have been identified in previous research, were not revealed as independent factors for the development of ICDs in our study [21,22].

CONCLUSION

As in conclusion, levodopa treatment offers a promising option for PD patients in the Shandong area. With increasing attention has been paid to clinical trials in China in the past 40 years, with the number and health burden of PD increased rapidly, more and more studies are needed to ensure better therapeutic outcomes in PD patients. Levodopa treatment offers a promising option for PD patients in the Shandong area. However, more studies with a larger sample are needed to further confirm the efficacy and safety of levodopa treatment in China.

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AUTHORS CONTRIBUTIONS

L. XU contributed to the study design, data collection and statistical analysis. L. XU and L. WANG contributed to the manuscript preparation. All authors read and approved the final version of the manuscript.

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