Article

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The Combined Use of Levodopa/Benserazide and Pramipexole Proves Beneficial for Managing Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD), a prevalent neurological condition, is characterized by the progressive degeneration of dopamine-producing neurons, leading to motor dysfunction and non-motor symptoms. Therefore, this study aimed to evaluate the impact of combining levodopa/benserazide with pramipexole on PD patients, focusing on cognitive function, plasma monoamine neurotransmitter levels, and serum growth differentiation factor-15 (GDF-15) and angiopoietin-1 (Ang-1) levels.

Methods: This retrospective study included 120 PD patients admitted to the hospital between January 2021 and January 2023. Based on the treatment approaches, the patients were categorized into the control group (n = 61) and the observation group (n = 59). The control group received oral levodopa/benserazide tablets, while the observation group was treated with levodopa/benserazide tablets combined with pramipexole. The two experimental groups were assessed and compared across several parameters, including PD symptoms [Unified Parkinson's Disease Rating Scale (UPDRS)], cognitive function [Montreal Cognitive Assessment (MoCA)], the levels of plasma monoamine neurotransmitters, and serum GDF-15 and Ang-1 levels.

Results: The response rate to treatment was more significant in the observation group (96.55%) compared to the control group (87.93%, $p = 0.162$). Post-treatment, both groups demonstrated a decline in their UPDRS and overall scores, with the observation group indicating substantially lower scores than the control group ($p < 0.05$). Furthermore, both groups showed improvements in MoCA scores, with the observation group exhibiting higher scores than the control group ($p < 0.05$). Similarly, we observed significantly increased dopamine, 5-hydroxytryptamine, and norepinephrine levels in both groups, with the observation group showing a more pronounced increase ($p < 0.05$). Additionally, we observed a significant decrease in serum GDF-15 levels and an increase in Ang-1 levels across both groups after treatment. However, the observation group exhibited lower GDF-15 levels and higher Ang-1 levels than the control group ($p < 0.05$).

Conclusions: The combined use of levodopa/benserazide and pramipexole proves beneficial for managing PD. This therapeutic regimen can improve cognitive abilities and plasma monoamine neurotransmitter levels in PD patients, reduce brain tissue damage and decrease serum levels of GDF-15.

Keywords

Parkinson's disease; levodopa/benserazide; pramipexole; cognitive function; plasma monoamine neurotransmitter

Introduction

Epidemiology shows that approximately 0.3% of the Chinese population is diagnosed with Parkinson's disease (PD) [1]. Furthermore, among individuals aged 65 and older, the incidence ranges from 1% to 2% [1]. PD, a progressive degenerative disease of the nervous system, lacks a definitive etiology; however, studies have indicated that it results from a complex interaction of certain factors, including genetics, age, environment, and oxidative stress [2,3].

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PD commonly occurs with substantial motor symptoms, including slowed movements, a fixed tremor, issues with postural stability, and muscle stiffness. Additionally, it includes non-motor symptoms like sensory deficiencies, cognitive decline, and mood disturbances such as depression and anxiety, with cognitive decline being particularly prevalent [4,5]. PD cognitive impairment is not characterized by forgetfulness, but mainly by cognitive abnormalities in attention, memory, language function, visuospatial and executive function [6].

Due to the unclear pathogenesis of PD, current clinical management is limited to symptomatic treatment and cannot effectively prevent or reverse the progression of disease. This limitation poses a significant challenge for existing PD therapeutic drugs [7]. PD treatment mainly targets the dopaminergic system [8]. It alleviates the adverse effects of dopaminergic neurodegeneration in patients by supplementing dopamine, stimulating dopamine receptors, and inhibiting dopamine decomposition [9,10].

Common drugs for PD can be divided into dopamine precursors, dopamine receptor agonists, peripheral catecholamine-O-methyltransferase inhibitors, as well as amantadines and anticholinergics that target other mechanisms [11–13]. Levodopa is the drug of choice for clinical PD treatment, as it effectively alleviates symptoms. However, the disease continues to progress, and long-term consumption of levodopa can lead to the death of dopamine-producing cells in the brain's substantia nigra, affecting its efficacy over time [14,15]. Benserazide, a monoamine oxidase B (MAO-B) inhibitor, improves symptoms by reducing the degradation of dopamine, thereby increasing its concentration in the brain [16]. Pramexol, a new generation of non-ergocline selective dopamine D_2 and D_3 receptor agonists, not only significantly improves the clinical symptoms in PD patients but also ensures drug safety and reduces adverse reactions [17,18].

Therefore, this study aimed to explore the impact of combining levodopa/benserazide with pramipexole on PD treatment, focusing on cognitive function, plasma monoamine neurotransmitter levels, and serum growth differentiation factor-15 (GDF-15) and angiopoietin-1 (Ang-1) levels. The goal was to provide a theoretical foundation for the medical management of PD.

Materials and Methods

Research Participants

This study included 120 PD patients admitted in the hospital between January 2021 and January 2023. The patients were categorized into two groups: the observation group and the control group. This study received approval from the Medical Ethics Committee of The Second Hospital of Nanjing, Nanjing University of Chinese Medicine (20210436) and was performed following the standards of the Helsinki Declaration. The study participants were enrolled using inclusion criteria as follows: (1) PD patients who met the China PD Diagnostic Criteria (2016 edition) [19], and (2) patients with stable vital signs who, along with their family members, provided signed informed consent forms. However, the exclusion criteria were set as below: (1) patients with dementia or schizophrenia, (2) those with a malignant tumor, (3) patients with allergies to the study drugs, (4) those with secondary PD, (5) patients participating in other research projects, and (6) those with a history of epilepsy. Additionally, the detachment criteria included: (1) patients who withdrew from the study for any reason, and (2) those who were not followed up.

Treatment Methods

Participants in the control group received doba serazid tablets (Sinophosphoric code H10930198, specification: 0.25 g, Shandong Xinhua Pharmaceutical Co., Ltd., Zibo, China) as oral treatment, with half a tablet 3 times a day. If symptoms did not improve after a week, the dose was increased to 0.25 g once, 3 times/day. The observation group was treated with pramexole tablets (imported, registration number H20140918, 0.25 mg, manufactured by Boehringer Ingelheim GmbH, Ingelheim, Germany). Like the control group, they started with half a tablet three times a day. After 1 week, the dosage was increased to 0.25 mg each time, 3 times/day. Both experimental groups continued their respective treatment for 3 months.

Outcome Indicators

Outcome indicators were assessed as follows:

(1) Unified Parkinson's Disease Rating Scale (UPDRS). To assess the symptoms of PD, the UPDRS was applied to both experimental groups before and after the treatment period [20]. This evaluation covered non-motor and motor symptoms. Non-motor symptoms included issues related to the autonomic nervous system, cognitive and men-

Table 1. Comparison of the baseline characteristics between the two experimental groups.

Characteristic	Observation group (n = 59)	Control group (n = 61)	t/χ^2-value	*p*-value
Gender (male)	28 (47.5%)	28 (45.9%)	0.029	0.864
Age (years)	62.64 ± 6.65	62.32 ± 7.43	0.247	0.806
Course of disease (years)	3.16 ± 0.47	3.20 ± 0.69	–0.354	0.724
Hoehn-Yahr stages			0.812	0.666
Stages I–II	8 (13.6%)	12 (19.7%)		
Stage III	17 (28.8%)	16 (26.2%)		
Stages IV–V	34 (57.6%)	33 (54.1%)		

tal health disturbances, sensory disruptions, and sleep disturbances. Motor symptoms included myotonia, postural and walking disturbances, consistent tremors, and bradykinesia, with a cumulative score of 44. Higher scores indicate greater severity of PD symptoms.

(2) Montreal Cognitive Assessment (MoCA). Cognitive functions were measured using the MoCA test [21]. This test was performed in both experimental groups before and after the treatment to determine changes in language, memory, attention and concentration, visual-spatial coordination, executive functions, and abstract reasoning. The MoCA test has a maximum score of 30, with 26 or above indicating normal cognitive functioning. In contrast, a score below 26 suggests cognitive impairment, with the degree of impairment increasing as the score decreases.

(3) Plasma monoamine neurotransmitter levels: Patients were instructed to avoid consuming foods with high tyramine content 3 days before blood collection. Blood samples (3 mL) were drawn from the venous region of the elbow during morning fasting sessions before and after the treatment period. Subsequently, these samples were centrifuged to collect plasma. Using American waters ACQUITY liquid phase system (Waters Corp., Milford, MA, USA), the UltiMate 3000 electrochemical detector (Ultimate 3000, Dionex, Sunnyvale, CA, USA) and the BF-2002 chromatographic workstation, 0.5 mL of plasma and an equal volume of extraction solution were mixed and shaken. After centrifugation at 4 °C at 18,000 r/min, 0.5 mL of supernatant was obtained followed by adding 0.2 mL buffer. Following centrifugation for 10 minutes, a 50 µL of supernatant was carefully collected to evaluate each neurotransmitter. Initially, dopamine (DA) levels were determined using a specific assay. Subsequently, serotonin levels, known as 5-hydroxytryptamine (5-HT), were measured through a separate test. Finally, norepinephrine (NE) concentrations were assessed utilizing a distinct method tailored for this compound.

(4) Serological indexes: The blood sample collection and centrifugation were similar as described above. Serum levels of Ang-1 and GDF-15 were assessed in the supernatant using corresponding enzyme-linked immunosorbent assay (ELISA) kits (CS476851 and CS488866), which were sourced from Shanghai Hengyuan Biotechnology Co., Ltd.

These scoring indicators were assessed by specially trained professionals. The raters were typically neurologists or researchers with extensive clinical experience in the diagnostic and treatment standards of Parkinson's disease. They have received training in the relevant scoring scales to ensure the accuracy and consistency of the ratings.

Criteria for Assessing Treatment Success

Treatment effectiveness was assessed as below: Markedly effective: The patients indicated significant improvement in cognitive abilities after treatment, with the UPDRS score reduced by ≥50%. Effective: After treatment, patients exhibited improvements in cognitive function, with a decrease in UPDRS scores between 20% and 50%. Ineffective: There was no improvement in cognitive function after treatment, and the UPDRS score decreased by <20% or even increased. Moreover, total effectiveness is the combined proportion of significantly effective and effective outcomes.

Methods for Data Analysis

Data were analyzed using IBM's SPSS 23.0 software (located in Armonk, NY, USA). Data following normal distribution were expressed using the mean and standard deviation, with comparisons conducted using either the independent samples *t*-test across different groups or the paired samples *t*-test within the same group. However, data that did not follow a normal distribution were expressed using the median and interquartile range, with analyses performed using the Mann-Whitney U test across groups or the Wilcoxon signed rank test within a single group. Categorical data were quantified by frequency and percentage, with the chi-square test or Fisher's exact test used for categories

Table 2. Assessment of treatment outcomes between the two experimental groups.

Experimental groups	*n*	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	58	35 (60.34)	21 (36.21)	2 (3.45)	56 (96.55)
Control group	58	24 (41.38)	27 (46.55)	7 (12.07)	51 (87.93)
χ^2-value					1.927
p-value					0.162

Table 3. Comparison of UPDRS scores pre- and post-treatment across both the experimental groups.

Items			Observation group (n = 58)	Control group (n = 58)	*t*/*Z*-value	*p*-value
Non-motor symptoms	Autonomic nervous dysfunction	Before treatment	5.18 ± 1.05	5.23 ± 1.24	0.234	0.815
		After treatment	2.08 ± 0.57*	3.19 ± 0.76*	8.898	<0.001
	Cognitive/mental disorders	Before treatment	4.82 ± 1.09	4.78 ± 1.52	0.163	0.871
		After treatment	2.16 ± 0.82*	3.24 ± 0.54*	8.377	<0.001
	Sensory disorders	Before treatment	5.08 ± 1.15	5.13 ± 1.36	0.214	0.831
		After treatment	2.18 ± 0.53*	3.06 ± 0.68*	7.773	<0.001
	Sleep disorders	Before treatment	5.49 ± 1.28	5.53 ± 1.57	0.150	0.881
		After treatment	1.00 (0.00, 2.00)*	3.00 (2.00, 4.00)*	7.529	<0.001
Motor symptoms	Myotonia	Before treatment	4.76 ± 1.58	4.72 ± 1.41	0.144	0.886
		After treatment	1.26 ± 0.48*	2.51 ± 0.43*	14.772	<0.001
	Postural and gait abnormalities	Before treatment	3.58 ± 1.14	3.53 ± 1.24	0.226	0.822
		After treatment	1.34 ± 0.53*	2.84 ± 0.95*	10.501	<0.001
	Static tremor	Before treatment	4.15 ± 1.04	4.19 ± 1.13	0.198	0.842
		After treatment	2.07 ± 0.56*	3.61 ± 0.82*	11.811	<0.001
	Bradykinesia	Before treatment	4.27 ± 1.24	4.31 ± 1.36	0.166	0.869
		After treatment	1.86 ± 0.54*	2.58 ± 0.76*	5.881	<0.001
Total score		Before treatment	37.04 ± 2.82	37.53 ± 2.72	0.952	0.343
		After treatment	13.75 ± 2.43*	24.19 ± 2.52*	22.712	<0.001

Note: * denotes a comparison with the group's scores before treatment, indicating a significant difference with a *p*-value less than 0.05; UPDRS, Unified Parkinson's Disease Rating Scale.

with expected frequencies below five to maintain statistical integrity. A *p*-value of less than 0.05 was regarded as indicative of statistical significance.

Results

Comparison of the Baseline Characteristics between the Two Experimental Groups

A comparison of the baseline characteristics between the observation group (59 patients) and the control group (61 patients) is shown in Table 1. The observation group included 28 males and 31 females, with an average age of 62.64 years. The average duration of illness was 3.16 years. The Hoehn-Yahr stage distribution was as below: 8 patients in stages I to II, 17 in stage III, and 34 in stages IV to V. Moreover, the control group consisted of 28 males and 33 females, with an average age of 62.32 years. The average duration of illness in this group was 3.20 years. The Hoehn-Yahr stage distribution in the control group included 12 patients in stages I to II, 16 in stage III, and 33 in stages IV to V. Statistical analysis indicated no significant differences in baseline characteristics between the two experimental groups ($p > 0.05$).

Assessment of Treatment Outcomes between the Two Experimental Groups

One participant withdrew from the study during the treatment process and three others discontinued it. Consequently, 58 patients from the observation group and 58 from the control group completed the study. As shown in Table 2, the treatment was effective for 96.55% of the observation group and 87.93% of the control group. However, this difference in efficacy between the two experimental groups was not statistically significant ($p = 0.162$).

Table 4. Evaluation of MoCA scores before and after treatment across the two experimental groups.

Variables		Observation group (n = 58)	Control group (n = 58)	*t*/*Z*-value	*p*-value
Attention and concentration	Before treatment	2.08 ± 0.49	2.13 ± 0.61	0.487	0.627
	After treatment	4.58 ± 1.06*	3.24 ± 1.21*	6.343	<0.001
Language	Before treatment	1.50 (1.00, 2.00)	1.51 (1.02, 2.05)	0.328	0.750
	After treatment	4.73 (3.74, 5.55)*	2.38 (1.36, 3.51)*	–6.924	<0.001
Memory	Before treatment	1.51 (1.01, 2.03)	1.53 (1.03, 2.01)	0.347	0.523
	After treatment	4.16 ± 1.23*	3.18 ± 1.08*	4.560	<0.001
Visual structure skills	Before treatment	2.53 ± 1.06	2.59 ± 1.13	0.295	0.769
	After treatment	4.61 ± 1.52*	3.18 ± 1.42*	5.236	<0.001
Executive ability	Before treatment	2.94 ± 1.04	2.91 ± 1.34	0.135	0.893
	After treatment	4.71 (4.01, 5.52)*	2.92 (2.03, 4.05)*	6.391	<0.001
Abstract thinking	Before treatment	2.17 ± 0.59	2.13 ± 0.84	0.297	0.767
	After treatment	4.18 ± 1.24*	3.51 ± 1.27*	2.875	0.005
Total score	Before treatment	12.74 ± 2.19	12.69 ± 2.54	0.159	0.874
	After treatment	27.11 ± 3.18*	18.49 ± 2.63*	15.908	<0.001

Note: * denotes a comparison with the group's scores before treatment, indicating a significant difference with a *p*-value less than 0.05; MoCA, Montreal Cognitive Assessment.

Table 5. Evaluation of plasma monoamine neurotransmitters before and after treatment across the two experimental groups.

Experimental groups	*n*	NE (ng/mL)		5-HT (pg/mL)		DA (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	58	485.53 ± 22.51	568.92 ± 21.46*	25.49 ± 4.08	49.18 ± 8.17*	43.85 ± 4.42	73.18 ± 8.49*
Control group	58	483.61 ± 23.57	532.76 ± 22.86*	24.41 ± 4.72	35.42 ± 7.24*	43.08 ± 5.19	61.82 ± 7.42*
t-value		0.449	8.783	1.318	9.600	0.860	7.673
p-value		0.655	<0.001	0.190	<0.001	0.392	<0.001

Note: * denotes a comparison with the group's scores before treatment, indicating a significant difference with a *p*-value less than 0.05; NE, norepinephrine; 5-HT, 5-hydroxytryptamine; DA, dopamine.

Comparison of UPDRS Scores Pre- and Post-Treatment across both Groups

As shown in Table 3, post-treatment observations indicated that scores for autonomic nervous dysfunction, cognitive/mental disorders, sensory disorders, sleep disorders, myotonia, postural and gait abnormalities, static tremor, bradykinesia, and the total score in the observation group were considerably lower compared to the control group ($p < 0.001$). Additionally, both the observation group and the control group exhibited significant reductions in these scores compared to their pre-treatment values ($p < 0.05$).

Evaluation of MoCA Scores before and after Treatment across the Two Experimental Groups

We observed that post-treatment, the scores for attention and concentration, language, memory, visual-spatial skills, executive ability, abstract thinking, and the cumulative score for the observation group were substantially higher compared to the control group ($p < 0.001$), with the abstract thinking score being superior to the control group ($p = 0.005$). Additionally, within both the observation and control groups, post-treatment evaluations revealed significant enhancements in attention and concentration, language abilities, memory, visual-spatial skills, executive functions, abstract reasoning, and overall scores compared to the baseline assessments before treatment ($p < 0.05$). The evaluation of MoCA scores is shown in Table 4.

Comparison of Plasma Monoamine Neurotransmitters before and after Treatment across the Two Experimental Groups

We observed that post-treatment, there was a substantial increase in the plasma levels of monoamine neurotransmitters (NE, 5-HT, and DA) in both the observation and control groups, with these levels being significantly higher compared to their pre-treatment values ($p < 0.05$). Furthermore, the observation group showed significantly elevated levels of these neurotransmitters compared to the control group following the treatment ($p < 0.001$, Table 5).

Table 6. Assessment of blood markers before and after treatment across the two experimental groups.

Experimental groups	*n*	Ang-1 (μg/L)		GDF-15 (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	58	12.48 ± 2.34	27.85 ± 2.16*	1185.07 ± 241.16	514.83 ± 124.46*
Control group	58	12.56 ± 2.49	22.27 ± 2.42*	1195.82 ± 234.52	784.92 ± 135.62*
t-value		0.178	13.101	0.243	11.175
p-value		0.859	<0.001	0.808	<0.001

Note: * denotes a comparison with the group's scores before treatment, indicating a significant difference with a *p*-value less than 0.05; Ang-1, angiopoietin-1; GDF-15, growth differentiation factor-15.

Assessment of Blood Markers before and after Treatment across the Two Experimental Groups

As shown in Table 6, there were significant post-treatment changes in Ang-1 and GDF-15 serum concentrations in both the observation and control groups ($p < 0.05$). However, post-treatment, the Ang-1 concentrations in the observation group were higher than those in the control group ($p < 0.001$), while the GDF-15 concentrations were significantly reduced compared to the control group ($p < 0.001$). Furthermore, both groups showed a significant increase in Ang-1 levels and a decrease in GDF-15 levels following treatment compared to their pre-treatment levels ($p < 0.05$).

Discussion

The findings from this study demonstrate that combining levodopa/benserazide tablets with pramipexole significantly improves clinical symptoms and cognitive function in patients with PD. PD is a progressive neurodegenerative condition characterized by the gradual loss of dopaminergic neurons in the nigrostriatal pathway, resulting in decreased dopamine levels in the striatum and an imbalance between dopamine and acetylcholine. This disruption causes various motor manifestations, including slowed movement (bradykinesia), resting tremors, postural and walking disturbances, and muscle stiffness (myotonia). Additionally, this imbalance contributes to non-motor-related issues, such as cognitive impairments, mental health conditions, autonomic nervous system dysfunction, and sensory perception disruptions. These diverse symptoms collectively influence the daily functioning and quality of life of affected individuals [22,23].

Currently, the primary treatment for PD involves levodopa/benserazide tablets, which increase dopamine levels in the brain by crossing the blood-brain barrier and converting to dopamine. While effective in controlling the disease and improving cognitive function, long-term use of these tablets can lead to side effects such as depression, insomnia, and decreased appetite. Additionally, its prolonged use may impair the regulatory function of neurons in the substantia nigra [24–26].

Pramipexole, a novel non-ergoline dopamine receptor agonist, has shown effectiveness in activating D_2 and D_3 receptors in the substantia nigra, providing high bioavailability and long-lasting effects [27,28]. Recent study has explored the combined use of pramipexole and levodopa/benserazide tablets for treating PD, primarily focusing on improving cognitive function [18]. In this study, we investigated the influence of dual therapy on both motor and non-motor manifestations in PD patients. Our findings indicated that the observation group receiving levodopa/benserazide and pramipexole had a significantly higher response rate (96.55%) than the control group (87.93%). After treatment, there was a significant decrease in UPDRS scores and overall scores, with the observation group (the combination therapy group) indicating a more pronounced reduction. Likewise, both groups exhibited substantial enhancements in MoCA scores and overall scores, with the observation group demonstrating more pronounced improvements. Plasma levels of DA, 5-HT, and NE also increased significantly in all participants, with more pronounced enhancements found in the observation group. These findings suggest that the combination therapy effectively enhances plasma monoamine neurotransmitter levels in PD patients [29]. The enhanced efficacy of this combination therapy may be attributed to the longer half-life of pramipexole, which allows prolonged stimulation of dopamine receptors in the substantia nigra, supports dopaminergic neuron protection, inhibits apoptosis, and reduces free radical formation. This extended neuroprotection likely contributes to the better clinical outcomes observed in patients [29].

Furthermore, we evaluated two biomarkers: GDF-15 and Ang-1. GDF-15, a member of the transforming growth factor β superfamily, typically increases in response to injury, oxidative stress, or inflammation, and has anti-inflammatory, anti-apoptotic and anti-growth effects [30].

Although GDF-15 is known to safeguard dopaminergic neurons in the nigrostriatal pathway, higher concentrations are linked to diminished cognitive function in dementia patients with PD [31]. Moreover, Ang-1 promotes angiogenesis and vascular stability, facilitating the establishment of collateral circulation [32]. Our findings showed a significant increase in serum Ang-1 levels in all patients following treatment, with more pronounced increases in the observation group. Conversely, GDF-15 levels decreased significantly, with lower levels in the observation group. These findings suggest that pramipexole may enhance angiogenesis and collateral circulation by reducing GDF-15 levels, thereby protecting nerve cells and improving cognitive function in PD patients.

Conclusions

In conclusion, the combined use of levodopa/benserazide and pramipexole shows substantial benefits in managing PD. This therapeutic approach enhances patients' cognitive abilities and elevates the concentrations of plasma monoamine neurotransmitters and Ang-1. Additionally, it contributes to the reduction of damage to brain tissues and lowers the serum levels of GDF-15. Based on these positive outcomes, this treatment regimen holds great promise for broader clinical adoption and utilization.

Availability of Data and Materials

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

Author Contributions

QL and WW designed the study and drafted the initial manuscript. HPW and SYL conducted the research. YYZ and YBZ conducted the research, provided assistance and suggestions, and revised the manuscript during the writing process. GYL analyzed the data. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for the study was obtained from the Medical Ethics Committee of The Second Hospital of Nanjing, Nanjing University of Chinese Medicine (20210436). Written informed consent was obtained from all participants and their family members.

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Conflict of Interest

The authors declare no conflict of interest.

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