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Therapeutic effect of levodopa-carbidopa-entacapone combined with rTMS in Parkinson's disease

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive tissue deterioration. This study evaluated the effects of levodopa-carbidopa-entacapone (LCE) combined with high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) in elderly PD patients. Participants were divided into an observation group (HF-rTMS + LCE) and a control group (HF-rTMS alone). Motor and cognitive function, quality of life, and adverse effects were assessed before treatment and at 8 weeks, 16 weeks, and 6 months post-treatment. Both groups showed no significant differences in baseline data. However, post-treatment, the observation group demonstrated superior clinical improvements. The Unified Parkinson's Disease Rating Scale-III (UPDRS-III) score significantly decreased from 43.40±3.94 to 34.73±5.05 at 6 months ($P<0.01$), while the Berg Balance Scale (BBS) score increased from 30.97±5.17 to 46.35±5.75 ($P<0.01$). The Timed Up and Go test (TUGT) time reduced from 13.12±2.23 seconds to 8.62±2.50 seconds ($P<0.01$), and the Parkinson's Disease Questionnaire (PDQ-39) score decreased from 37.32±3.69 to 25.75±4.59 ($P<0.01$). Additionally, the Montreal Cognitive Assessment (MoCA) score increased from 22.05±2.24 to 28.15±1.99 ($P<0.001$). Adverse effects were similar between groups (16.7% vs. 15%, $P>0.05$). These results suggest HF-rTMS combined with LCE enhances motor function, balance, cognition, and quality of life in elderly PD patients without increasing adverse effects.

Keywords: Levodopa, carbidopa, entacapone; transcranial magnetic stimulation; Parkinson's disease.

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INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by the progressive loss of dopamine neurons in the substantia nigra pars compacta. It is a neurological disease with one of the most rapidly increasing rates of morbidity and disability (Karikari *et al*., 2018). PD primarily affects middle-aged and elderly individuals, with its incidence rising significantly with age. The average age of onset is around 60 years, and the incidence of PD among individuals aged in the 65 and older is approximately 1.7% in China (Yuan *et al*., 2023). Due to the aging population, the number of PD patients in China has grown substantially, surpassing 1.7 million in 2016 (Chen F *et al*., 2022).

Currently, PD is mainly managed with drug therapy, particularly dopamine replacement therapy. Levodopa-carbidopa-entacapone (LCE) is a popular medication for the treatment of PD. However, if PD symptoms are not effectively controlled, the disease progresses with motor impairments such as tremors, bradykinesia, myotonia, postural instability and gait abnormality, alongside non-motor symptoms like cognitive dysfunction, depression, anxiety, urinary and fecal abnormalities and pain (Schrag *et al*., 2000; Marras *et al*., 2002; Muslimovic *et al*., 2008). These complications place a heavy financial burden on patients and society.

To complement drug therapy, adjuvant treatments like high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) have been introduced. HF-rTMS is a non-invasive treatment modality recognized for alleviating motor symptoms in PD patients and has shown promise in addressing PD-related depression and cognitive dysfunction. HF-rTMS has become a significant adjunctive treatment for PD in clinical practice (Kamble *et al*., 2014; Xie *et al*., 2015).

However, few clinical research investigated the combined use of LCE medication and HF-rTMS for treating PD. This study aims to evaluate the effects of this combined treatment on elderly PD patients, providing a potential new approach to enhancing their quality of life and reducing healthcare costs.

MATERIALS AND METHODS

Baseline information

This study retrospectively included 120 elderly PD patients admitted to Huaian Traditional Chinese Medicine Hospital from January 2022 to January 2023, all of whom were given HF-rTMS. These patients were assigned to

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receive HF-rTMS alone (control group, n=60) or HF-rTMS combined with LCE (observation group, n=60). General data including sex, age, education level, disease duration and Hoehn-Yahr staging were collected from both groups.

Inclusion and exclusion criteria

Inclusion criteria were outlined below: (1) Diagnosis of primary PD based on the clinical diagnostic criteria established by the Parkinson's UK Brain Bank; (2) Hoehn-Yahr staging between 1.0 and 3.0, indicating mild to moderate disease severity; (3) Age ≥65 years at the time of enrollment; (4) No use of antidepressant medication for at least 2 weeks prior to treatment initiation to avoid confounding effects on motor and cognitive assessments; (5) Availability of complete and accurate clinical data.

Exclusion criteria were as detailed below: patients (1) Diagnosed with Parkinson-plus syndrome or secondary parkinsonism caused by toxins, hydrocephalus, trauma, vascular lesions, tumors, or genetic factors; (2) Known allergy or hypersensitivity to any component of the LCE combination therapy; (3) History of psychiatric disorders or depression; (4) Pre-existing underlying limb dysfunction; (5) Coexisting liver, kidney and other organ lesions; (6) Presence of tumors or other major diseases; (7) Systemic diseases in a stage of decompensation.

Grouping and treatment methods

Both groups received HF-rTMS and the observation group was given LCE in addition to HF-rTMS.

HF-rTMS protocal: Using the Magneuro 60 transcranial magnetic stimulator (Nanjing Vishee Medical Technology Co Ltd) and fig. -eight coils, all patients were instructed to lie relaxed. Treatment procedures and precautions were explained beforehand for optimal cooperation. Patients were advised not to move their fingers intentionally during treatment. The coil center was positioned over the left hemisphere's F3 area. Stimulation intensity was gradually increased to reach the motor threshold, defined as the minimum intensity causing visible movement in the right thumb. Stimulation parameters were then set at 110% of the motor threshold, with a frequency of 10 Hz. Each session included continuous stimulation for 5 seconds, followed by a 30-second rest, totaling 20 minutes per session, conducted daily over an 8-week period (14 days per treatment course).

LCE medication: LCE tablets (Orian Pharma Ltd., Finland; 100mg levodopa, 25mg carbidopa, 200mg entacapone) were administered orally, one tablet an hour before each meal (three times daily). The medication course was 4 weeks, repeated for 4 courses.

Observation and evaluation indicators

Related indicators of all participants were evaluated before intervention and 8 weeks, 16 weeks and 6 months after intervention.

Motor function

Unified Parkinson's Disease Rating Scale-III (UPDRS-III) was employed in evaluating patients' motor function (Fahn and Elton 1987). This scale evaluates 14 items across multiple domains, including tremor, rigidity, bradykinesia and postural instability. Each item was scored on a scale of 0 (no impairment) to 4 (severe impairment), with a higher total score indicating more severe impaired motor function. Evaluations were conducted by trained neurologists to ensure consistency and accuracy.

Balance function

Berg balance scale (BBS) (Scherfer *et al*., 2006) was responsible for assessing the overall balance function. It consists of 14 tasks, such as sitting to standing, sanding with eyes closed, turning 360 degrees, and tandem standing. Each task is scored on a 5-point scale (0 = unable to perform, 4 = performs independently), with a maximum total score of 56. Higher BBS score indicates better balance.

Walking ability

Timed Up and Go test (TUGT) (Karuka *et al*., 2011) was performed to measure patients' walking ability. The procedure involved the patient standing up from a standard chair, walking 3 meters, turning, and returning to sit in the chair. The total time to complete the test was recorded, with times >16 s indicating increased risk of fall. Patients performed the test under the supervision of trained rehabilitation specialists to ensure safety.

Cognitive function

Cognitive function was assessed with the help of Montreal Cognitive Assessment (MoCA) (Nasreddine *et al*., 2005), a 30-point screening tool designed to detect mild cognitive impairment. Tasks include visuospatial abilities, memory, attention, language, abstraction and executive function. A score ≤25 indicates mild cognitive impairment

Quality of life

Quality of life was measured using the Parkinson's Disease Questionnaire-39 (PDQ-39), which evaluates the impact of PD on daily life across eight dimensions, including mobility, emotional well-being, stigma and cognition (Peto *et al*., 1995). Each item is scored from 0 (no problem) to 4 (maximum problem) and higher scores reflect lower quality of life.

Adverse effects

Adverse effects were systematically recorded at each evaluation time point. Patients and their families were asked to report any symptoms, including headache, dizziness, rash, nausea and other complications. The overall incidence of adverse effects was compared between the two groups.

Table 1: Comparison of baseline data between the two groups of patients

	Control group (n = 60)	Observation group (n = 60)	*P*
Gender (men/women)	31/29	30/30	0.855
Age	62.42±4.57	61.87±4.64	0.514
Disease duration	6.07±1.46	6.00±1.37	0.797
Hoehn-Yahr staging			0.892
1.0	19 (31.7)	19 (31.7)	
1.5	9 (15.0)	8 (13.3)	
2.0	24 (40.0)	22 (36.7)	
2.5	8 (13.3)	11 (18.9)	

Data were expressed as mean ± SD or frequency (%).

Table 2: Comparison of cognitive function of patients between the Control and Observation groups

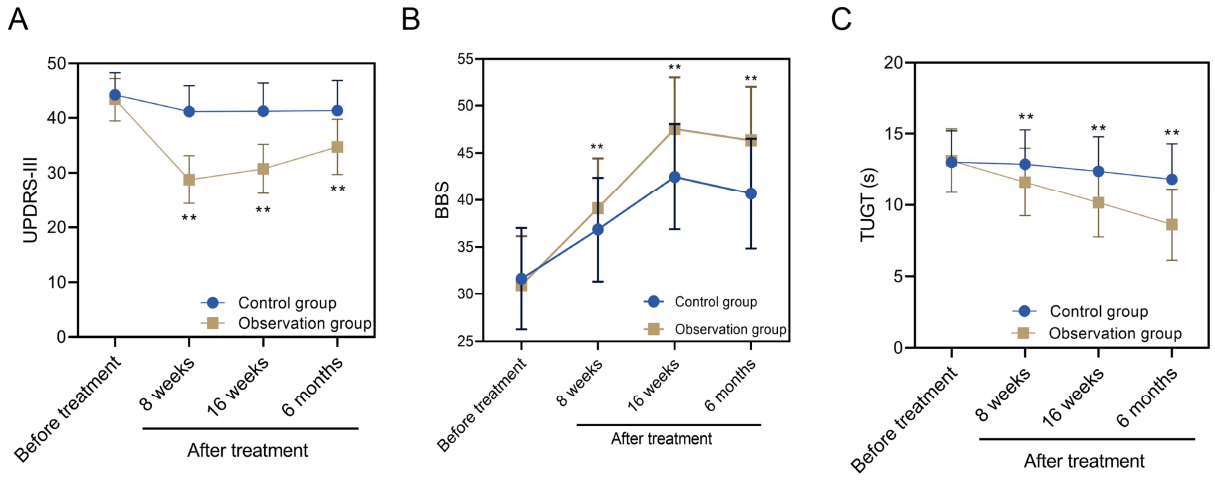
	MoCA	
	Before treatment	Six months after treatment
Control group	22.45±1.85	25.40±2.17
Observation group	22.05±2.24	28.15±1.99
P	0.289	<0.001

MoCA, Montreal Cognitive Assessment. Data were expressed as mean ± SD.

Table 3: Comparison of adverse reactions of patients between the Control and Observation groups

	Control group (n = 60)	Observation group (n = 60)	*P*
Nausea	1 (1.7%)	1 (1.7%)	1.000
Dyskinesia	1 (1.7%)	1 (1.7%)	1.000
Dizziness	2 (3.4%)	2 (3.4%)	1.000
Cephalalgia	1 (1.7%)	2 (3.4%)	0.559
Diarrhea	1 (1.7%)	1 (1.7%)	1.000
Tension	0 (0.0%)	1 (1.7%)	0.315
Insomnia	0 (0.0%)	1 (1.7%)	0.315
Asthenia	0 (0.0%)	1 (1.7%)	0.315
Celialgia	1 (1.7%)	0 (0.0%)	0.315
Fatigue	1 (1.7%)	0 (0.0%)	0.315
Dorsalgia	1 (1.7%)	0 (0.0%)	0.315
Incidence of adverse effects	9 (15.0%)	10 (16.7%)	0.803

Data were expressed as frequency (%).



(A) Unified Parkinson's Disease Rating Scale-III (UPDRS-III) evaluation of motor function of patients. (B) Berg balance scale (BBS) evaluation of the overall balance function of patients. (C) Timed Up and Go test (TUGT) evaluation of walking ability of patients.

Fig. 1: Comparison of motor function between two groups of patients.

Ethical approval

The study was approved by the Ethics Committee of Huaian Traditional Chinese Medicine Hospital (Ethics Approval No. K201-08). All patients and their families provided written informed consent before participation in the study.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 25.0 software. Normal-distributed measurement data were reported as mean ± standard deviation and an independent sample t-test was recruited for comparing the groups. Non-normally distributed data were expressed as median (Q25, Q75), with group comparisons performed utilizing Mann-Whitney U test. Categorical data were displayed presented as frequency (%), with chi-square test or Fisher's exact test for comparisons between groups. $P<0.05$ represented the statistical significance threshold.

RESULTS

Baseline information

Table 1 demonstrated the basic characteristics of the two patient groups. The control group (n = 60) consisted of 31 males and 29 females, with an average age of 62.42± 4.57 years and a disease duration of 6.07±1.46 years. Among the 60 participants in the observation group (30 males and 30 females), the average age was 61.87±4.64 years, and the disease duration was 6.00±1.37 years. Comparison of baseline data in the two groups indicated no notable difference ($P>0.05$). These results indicated that the two groups were comparable prior to intervention.

Comparison of motor function between the two groups

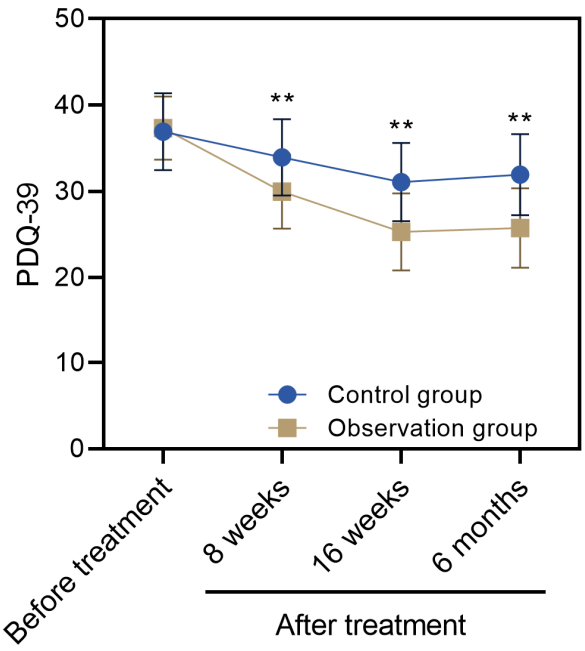
Assessment of motor function was achieved using UPDRS-III, BBS, and TUGT. Before treatment, there were no significant differences between the two groups for any of these measures ($P>0.05$). However, post-treatment, both groups exhibited different degrees of improvement in motor function and the observation group exhibited significantly greater improvements compared to the control group. Specifically, patients receiving HF-rTMS combined with LCE had a significant decline in UPDRS-III score, a significant increase in BBS score, and a shortening of TUGT time after 16 weeks of treatment in comparison with those given HF-rTMS alone (fig. 1A-C, $P<0.05$). These results denoted that HF-rTMS combined with LCE provided synergistic effects, likely enhancing dopaminergic signaling and improving motor function, balance, and gait to a greater extent than HF-rTMS alone.

Comparison of quality of life between the two groups

PDQ-39 was responsible for assessing the quality of life of individuals with PD. Baseline PDQ-39 scores were comparable between the observation and control groups (37.32±3.69 vs. 36.9±4.48, $P>0.05$). After treatment, both groups showed significant reductions in PDQ-39 scores, with the observation group experiencing a more substantial improvement. As showed in fig. 2, the observation group's PDQ-39 score decreased from 37.32 ±3.69 to 25.75±4.59, compared to a reduction from 36.90 ±4.48 to 31.93±4.69 in the control group ($P<0.001$). These findings indicated that the combined therapy not only improved motor function but also had a greater positive impact on patients' quality of life by alleviating physical and emotional burdens associated with PD.

Comparison of cognitive function between the two groups

Cognitive function was evaluated using MoCA (table 2). At baseline, MoCA scores were similar between the two groups (22.45±1.85 vs. 22.05±2.24, $P>0.05$). At the 6th month upon treatment, the MoCA score in the observation group increased to 28.15±1.99, which was significantly higher than that in the control group (25.40±2.17) ($P<0.001$). These improvements in the observation group may reflect enhanced dopaminergic activity and neuroplasticity facilitated by the combination of HF-rTMS and LCE, aligning with previous evidence that HF-rTMS promotes cognitive recovery by modulating prefrontal dopamine pathways (Chen *et al*., 2024).



Quality of life was assessed using Parkinson's Disease Questionnaire-39 (PDQ-39).

Fig. 2: Comparison of quality of life before and after treatment in two groups of patients.

Comparison of incidence of adverse effects after treatment between the two groups

As demonstrated in table 3, the incidence of adverse effects was low and comparable between the two groups (16.7% vs. 15%, $P>0.05$). Adverse effects included nausea, dizziness, headache and mild insomnia and no

severe adverse events were reported in either group. These results suggest that HF-rTMS combined with LCE is a safe therapeutic approach for elderly PD patients.

DISCUSSION

This study evaluated the effects of HF-rTMS combined with LCE therapy compared to HF-rTMS alone in PD patients, focusing on motor function, cognitive function, quality of life, and incidence of adverse effects. The combined therapy demonstrated superior improvements in motor function, balance, walking ability, cognitive competence, and quality of life, with no significant increase in the incidence of adverse effects. These findings suggested that the combination of HF-rTMS and LCE provided a synergistic therapeutic benefit for PD patients.

The observed benefits of HF-rTMS are consistent with its known ability to modulate neurotransmitter systems and promote neuroplasticity (Chen X *et al*., 2024). HF-rTMS over the motor cortex or dorsolateral prefrontal cortex has been shown to influence monoamine release, especially dopamine, within connected cortical and sub cortical regions (Cho and Strafella 2009). When applied to the prefrontal cortex, it may stimulate glutamatergic neurons and increase the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which supports synaptic plasticity and motor recovery (Brunoni *et al*., 2008). Previous studies have demonstrated that the efficacy of HF-rTMS in improving both motor and non-motor symptoms in PD, including depression and cognitive dysfunction (Michael *et al*., 2022; Wang *et al*., 2024).

LCE, a combination of levodopa, carbidopa and entacapone, addresses the core dopaminergic deficits of PD by increasing systemic dopamine levels. This is achieved through the inhibition of peripheral dopamine metabolism via dopa decarboxylase and catechol-O-methyltransferase pathways (Li *et al*., 2017; Senek *et al*., 2017). LCE alleviates motor symptoms, reduces functional impairments and decreases the occurrence of motor complications associated with levodopa monotherapy. The complementary mechanisms of HF-rTMS and LCE likely explain the superior outcomes observed in the combined therapy group. HF-rTMS enhances dopamine release in targeted brain regions, while LCE ensures sufficient dopamine availability to sustain these effects.

In this study, the combined therapy achieved significant improvements in motor function, as evidenced by the reduction in UPDRS-III scores. This reflects substantial alleviation of motor symptoms such as tremor, rigidity, and bradykinesia, which are critical for reducing disability and improving independence. The combination of HF-rTMS and LCE amplifies dopaminergic signaling, enhancing the effectiveness of neuromodulation on motor network connectivity. Additionally, the improvements in balance and walking ability, as reflected by higher BBS scores and shorter TUGT times, further highlight the multidimensional benefits of the combined therapy. Faster TUGT times, which fell below the clinically significant threshold of 16 seconds, suggest reduced fall risk and greater mobility, particularly important for elderly PD patients. These findings align with previous research suggesting that LCE improves gait and HF-rTMS enhances motor control through increased neural plasticity (Liao *et al*., 2020; Thanakamchokchai *et al*., 2020).

Cognitive improvements, as indicated by increased MoCA scores, were more pronounced in the combined therapy group compared to HF-rTMS alone. Cognitive deficits in PD are often linked to dopaminergic dysfunction in the prefrontal cortex (Nasreddine *et al*., 2005; King *et al*., 2015). HF-rTMS targets this region, stimulating dopamine release and improving executive function (Pal *et al*., 2010). LCE may further enhance this effect by addressing dopamine-dependent cognitive processes. Furthermore, the observed reduction in PDQ-39 scores highlights broader improvements in quality of life, including emotional well-being, mobility and social interaction. These findings emphasize the importance of addressing both motor and non-motor symptoms to achieve comprehensive therapeutic benefits for PD patients. The synergy between HF-rTMS and LCE likely contributes to these outcomes by targeting multiple aspects of PD pathology.

Importantly, the safety profile of the combined therapy was favorable, with a low incidence of mild adverse effects, such as dizziness and headache, and no severe adverse events reported. Among the reported adverse effects, 3.4% of patients experienced mild dizziness, 1.7% reported diarrhea and 1.7% had mild nausea, all of which resolved without intervention. The comparable rates of adverse events between the two groups (16.7% vs. 15.0%) suggest that the addition of LCE does not compromise the safety of HF-rTMS. However, the potential cumulative effects of long-term HF-rTMS sessions and LCE therapy require further investigation.

In addition, to ensure the reliability and robustness of the findings, we applied professional software and appropriate methods for statistical analysis. Continuous variables, such as UPDRS-III, BBS, TUGT, MoCA, and PDQ-39 scores, were compared using independent t-tests between groups. Chi-square tests were applied to analyze categorical data, such as adverse event rates. The observed statistical significance ($P<0.05$) underscores the consistency of the combined therapy's superior outcomes. Despite the promising results, this study has some limitations. Firstly, the relatively small sample size and single-center design may limit the generalizability of the

findings. Secondly, baseline data were limited to key demographic and clinical characteristics. Expanding baseline variables, such as comorbidities and prior treatment history, would provide greater context for interpreting the results. Thirdly, the fixed-dose combination of LCE used in this study reflects current clinical practice but does not explore the potential benefits of alternative drug ratios or personalized dosing strategies. Additionally, this study included only mild to moderate PD patients with Hoehn-Yahr stages ≤3.0, future research should explore the efficacy of the combined therapy in advanced PD stages to determine the broader applicability of this treatment approach. Finally, the study did not differentiate between specific non-motor symptoms, such as depression and anxiety, which are prevalent in PD and could influence quality-of-life outcomes. Therefore, future research should include larger, multicenter trials with more comprehensive data collection and explore the long-term efficacy and safety of HF-rTMS combined with LCE therapy.

CONCLUSION

HF-rTMS combined with LCE medication was superior to the application of HF-rTMS alone. Specifically, the combination treatment performed well for the outcomes and quality of life of elderly patients with PD through strengthening motor function, balance function, walking ability, and cognitive competence without increasing the incidence of post-treatment adverse effects.

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