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Age as a risk factor for orthostatic hypotension induced by the levodopa challenge test in patients with Parkinson's disease

Results from a single-center trial

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Abstract

Background: Hypotension can occur in patients receiving levodopa (L-dopa) treatment for parkinsonism. However, only few studies have focused on the characteristics of orthostatic hypotension (OH) induced by the L-dopa challenge test (LCT). This study aimed to investigate the characteristics and influencing factors of LCT-induced OH in a relatively large sample of patients with Parkinson's disease (PD).

Methods: Seventy-eight patients with PD without a previous diagnosis of OH underwent the LCT. Blood pressure (BP) in the supine and standing positions was measured before and 2 hours after the LCT. If diagnosed with OH, the patients' BP was monitored again 3 hours after the LCT. The clinical features and demographics of the patients were analyzed.

Results: Eight patients were diagnosed with OH 2 hours after the LCT (median dose of 375 mg L-dopa/benserazide; incidence = 10.3%). One patient without symptoms had OH 3 hours after the LCT. Compared with patients without OH, patients with OH had lower 1- and 3-minutes standing systolic BP and 1-minute standing diastolic BP at baseline and 2 hours after the LCT. Patients in the OH group were of older age (65.31 ± 4.17 years vs 59.74 ± 5.55years) and had lower Montreal Cognitive Assessment scores (17.5 vs 24) and higher L-dopa/benserazide levels (375 [250, 500] mg vs 250 [125, 500] mg). Older age markedly increased the odds of having LCT-induced OH (odds ratio, 1.451; 95% confidence interval, 1.055–1.995; P = .022).

Conclusions: LCT increased the odds of OH in non-OH PD, causing symptomatic OH in 10.3% of patients in our study, thereby raising safety concerns. Increase in age was observed to be a risk factor for LCT-induced OH in PD patients. A study with a larger sample size is warranted to confirm our results.

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Abbreviations: BP = blood pressure, LCT = levodopa challenge test, MAO-B = monoamine oxidase B, MoCA = Montreal Cognitive Assessment, OH = orthostatic hypotension, PD = Parkinson's disease.

Keywords: age, levodopa challenge test, orthostatic hypotension, Parkinson's disease

1. Introduction

Parkinson's disease (PD) is a common degenerative condition of the nervous system that occurs in approximately 1% of the population aged ≥ 65 years.[1] Over 3 million patients with PD have been reported in China alone.[2] There is some indication of an increase in the incidence of PD in some high-income countries.[3] PD is associated with high risk of disability, which is largely linked to the non-motor symptoms in PD and are difficult to manage. One of the most common non-motor symptoms in PD is orthostatic hypotension (OH) which in general refers to a sudden drop in blood pressure (BP) while standing up from a supine or sitting position. Impaired autonomic function is the primary cause of OH in patients with PD. An estimated 30% to 60% of patients with PD have OH,[4] which can occur in all stages of PD. Patients with OH are usually at a greater risk of falls and increased negative outcomes, including poor quality of life and mortality.[5,6]

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

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Levodopa (L-dopa) is a fundamental pharmacotherapy for management of PD symptoms. As the disease progresses, the effect of L-dopa on patient's BP should be closely monitored because anti-parkinsonian drugs, such as L-dopa, influence BP in patients with PD. Although L-dopa has often been reported to cause OH, some studies have reported inconclusive findings. Jost et al[7] reported merely a minor association between L-dopa and OH in individual PD cases. Pursiainen et al[8] revealed no marked differences in BP, regardless of L-dopa administration. Paradoxically, some other studies have reported OH attributed to increased L-dopa doses in a short time.[9,10]

Hyperresponsiveness to dopaminergic drugs is an important characteristic of PD. Drug stimulation tests, such as the acute levodopa challenge test (LCT), designed to acutely stimulate central dopaminergic receptors[11] can be applied to predict sustained long-term L-dopa responsiveness.[12] In recent years, some studies evaluated the influence of L-dopa on BP in patients with PD through LCT; however, the conclusions were also found to be contradictory. Evidence from previous studies show that there is still a large gap in the literature regarding OH and the use of L-dopa. The characteristics of L-dopa responsiveness in PD appear to be elusive. Very few studies have investigated the relationship between LCT and OH.[9,10]

Therefore, this study aimed to investigate the characteristics and influencing factors of OH induced by LCT in a relatively large sample of patients with PD. The outcomes of this study may improve our understanding of OH in PD and eventually help in its prevention or management.

2. Materials and methods

2.1. Participants

In this study, we enrolled 36 patients with early-onset PD (average age 54.2 ± 2.3 years) and 42 patients with idiopathic PD (average age 67.4 ± 4.7 years) from the Movement Disorder Clinic at the Department of Neurology, Xuanwu Hospital, Beijing. PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic criteria.[13]

The exclusion criteria were as follows: previously diagnosed OH; presence of other central nervous system diseases; secondary parkinsonism; history of hypertensive emergency or malignant hypertension; severe complications or diseases involving major organs such as liver and kidney dysfunction, cardiac insufficiency, respiratory failure; and malignant tumor.

The study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent for participating in this study. The study was approved by the Ethics Committee of Xuanwu Hospital (Clinical Drug Review [2021] No. 026).

2.2. Clinical evaluations

The included patients were on stable medication before undergoing LCT (68 patients received L-dopa, 28 received amantadine, 29 received dopamine agonists, 9 were treated with monoamine oxidase B [MAO-B] inhibitors, and 5 used a catechol-o-methyltransferase inhibitor). Their demographic data, history of hypertension, use of antihypertensive drugs, age of onset, Hoehn and Yahr stage, disease duration, and use of anti-PD drugs were recorded. The L-dopa equivalent daily dose was calculated using a formula described previously.[14] Clinical features were assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale. Motor phenotypes were divided into postural instability and gait difficulty-dominant and non-postural instability and gait difficulty-dominant based on the Movement Disorder Society Unified Parkinson's Disease Rating Scale scores.[15] Validated scales, including cognitive functions by the Montreal Cognitive Assessment (MoCA)-Beijing version,[16] anxiety by the Hamilton Anxiety Scale,[17] depression by the Hamilton Depression Scale,[18] quality of life by the 39-item Parkinson's Disease Questionnaire,[19] autonomic functions by the Non-Motor Symptoms Questionnaire,[20] and sleep problems by the Parkinson's Disease Sleep Scale,[21] were applied to evaluate patients' non-motor symptoms.

2.3. Levodopa challenge test

The LCT was implemented at the hospital in the morning after discontinuing all anti-PD drugs (L-dopa for at least 12 hours and dopamine agonists for at least 36 hours before the test) in a state of fasting. Antihypertensive drugs were discontinued simultaneously. The dose required for the trial was converted to 150% of conventional morning L-dopa equivalents.[22] Patients received L-dopa/benserazide equivalent to the calculated dose. Symptoms of discomfort, including dizziness, lethargy, fatigue, and nausea experienced by the participants were recorded during LCT.

All participants were assessed using the UPDRS-III at various time intervals: baseline and 0.5, 1, 2, and 3 hours after the initiation of LCT. In this study, 70 (89.7%) patients demonstrated the highest rate of improvement in motor symptoms, and highest subjective improvement score was observed 2 hours after receiving L-dopa/benserazide tablets (200 mg levodopa/50 mg benserazide, Shanghai Roche Pharmaceuticals Ltd, Shanghai, China). Therefore, the baseline UPDRS-III, LCT 2 hours UPDRS-III, and maximum improvement rate were used as observation indicators for this study.

2.4. BP measurement

BP was measured on the morning of the scheduled LCT and repeated 2 hours after the initiation of LCT using a certified blood pressure monitoring device (OmronHEM-7051, Kyoto, Japan). BP measurement was performed in all patients after 10 minutes of rest in a quiet and comfortable environment, first in the supine position and again within 1 to 3 minutes in an upright position. In patients who experienced OH 2 hours after the LCT, BP was measured again 1 hour after OH onset. As defined by the American Academy of Neurology and the American Society of Autonomic Neurology, OH was diagnosed following a decrease in systolic BP ≥ 20 mm Hg (1 mm Hg = 0.133 kPa) and/or diastolic BP ≥ 10 mm Hg within 3 minutes of being in an upright position.[23]

2.5. Statistical analyses

BP parameters were compared between patients with and without LCT-induced OH using the *t* test. The Mann–Whitney *U* test and chi-square test were used to analyze the non-normally distributed data and categorical values, respectively. The paired *t* test was used to compare BP parameters in patients with OH at different times. We performed a multivariate logistic regression analysis using age, MoCA score, L-dopa/benserazide dose, baseline 1 minute standing BP, and baseline 3 minutes standing systolic BP as independent variables. The risk factors were further analyzed using multiple logistic regression. The results are presented as mean ± standard deviation or median (minimum, maximum) for continuous variables and frequency (percentage) for categorical values. Significance was set at $P < .05$. SPSS (version 22.0; SPSS Inc., Chicago, IL) was used to perform analyses.

3. Results

3.1. Clinical characteristics of the patients

A total of 78 patients with parkinsonism participated in this study, and their clinical and demographic characteristics are shown

in Table 1. Sixty-eight patients received L-dopa, of whom 58 used L-dopa/benserazide and 8 additionally used controlled-release L-dopa/carbidopa, whereas 2 received controlled-release L-dopa/carbidopa alone. Amantadine was administered to 28 patients and dopamine agonists to 29 (pramipexole in 18 and piribedil in 11). Among the nine patients treated with MAO-B inhibitors, five received selegiline and four received rasagiline. Only five patients used a catechol-o-methyltransferase inhibitor (entacapone).

3.2. BP in patients with OH induced by the LCT

None of the participants presented with OH at baseline. Eight (occurrence 10.3%, average age was 65.31 ± 4.17 years) patients presented with OH 2 hours after the LCT. All patients presented with clinical symptoms (including dizziness in four patients, lethargy in two, and nausea in two), which was observed in four patients within 1 minute in the standing position, three within 3 minutes in the standing position, and one in the supine position. These symptoms gradually resolved after sitting at rest. The BP of these eight patients was monitored again 3 hours after the LCT.

The baseline 1-minute standing systolic BP (109.63 ± 27.86 vs 132.87 ± 20.43, $P < .001$), baseline 1-minute standing diastolic BP (70.13 ± 17.99 vs 80.13 ± 11.18, $P = .044$), and baseline 3-minutes standing systolic BP (126.50 ± 34.57 vs 136.20 ± 18.64, $P = .044$) was lower in patients with LCT-induced OH than in those without OH (Fig. 1).

Table 1

Clinical characteristics of the patients with Parkinson's disease (n = 78).

Characteristics	Total
Male (n, %)	46 (58.9)
Female (n, %)	32 (41.1)
Age (yr)	62.25 ± 5.21
Disease duration (yr)	6 (3, 11)
Hoehn–Yahr stage	
Early (n, %)	33 (42.3)
Middle (n, %)	20 (25.6)
Late (n, %)	25 (32.1)
PIGD dominant	48 (61.5)
Body mass index (kg/m^2)	23.43 ± 2.53
HAMA score	7.56 ± 3.49
HAMD score	7.98 ± 6.90
PDQ-39 score	31.11 ± 22.62
NMSQ score	29.00 ± 20.92
PDSS score	11.51 ± 9.68
MoCA score	22.40 ± 4.59
LEDD (mg)	400 (187.5, 865)
UPDRS-II score	13.29 ± 5.50
UPDRS-III score (Baseline)	34.29 ± 14.61
UPDRS-III score (2 h LCT)	23.47 ± 12.11
History of hypertension (n, %)	30 (38.5)
Levodopa/benserazide dose (mg)	280.68 ± 83.22
Maximum-improvement rate (%)	45.98 ± 11.41
Antihypertensive drugs (n, %)	20 (68.2)
Anti-PD drugs	
Levodopa (n, %)	68 (87.3)
Dopamine agonists (n, %)	29 (37.2)
Amantadine (n, %)	28 (35.9)
MAO-B inhibitors (n, %)	9 (11.5)
COMT inhibitors (n, %)	5 (6.4)

COMT = catechol-o-methyltransferase, HAMA = Hamilton Anxiety Scale, HAMD = Hamilton Depression Scale, LCT = levodopa challenge test, LEDD = L-dopa equivalent daily dose, MAO-B = monoamine oxidase B, MoCA = Montreal Cognitive Assessment-Beijing version, NMSQ = Non-Motor Symptoms Questionnaire, PD = Parkinson's disease, PDQ-39 = 39-item Parkinson's Disease Questionnaire, PDSS = Parkinson's Disease Sleep Scale, PIGD = postural instability/gait difficulty, UPDRS = Unified Parkinson's Disease Rating Scale.

The 1-min standing systolic BP (100.25 ± 17.69 vs 127.38 ± 24.79, $P < .001$), 1-minute standing diastolic BP (73.29 ± 12.51 vs 76.58 ± 13.85, $P = .043$), and 3-minutes standing systolic BP (96.92 ± 10.61 vs 120.53 ± 18.15, $P = .025$) 2 hours after the LCT were lower in patients with LCT-induced OH than in those without OH (Fig. 1).

Changing from supine to standing positions, patients with OH had a reduced mean systolic BP of 14 and 21 mm Hg at 1 and 3 minutes, respectively, 2 hours after the LCT. Similarly, the mean diastolic BP decreased by 6.5 and 13 mm Hg at 1 and 3 minutes, respectively, 2 hours after the LCT. In the non-OH group, mean systolic BP decreased by 8 and 5 mm Hg, while mean diastolic BP increased by 6 and 4 mm Hg at 1 and 3 minutes, respectively, 2 hours after the LCT (Fig. 2).

BP was monitored again in eight patients with OH 3 hours after the LCT. After 1 hour, all patients had no symptoms, and only one patient's BP met the OH diagnostic criteria. From baseline to 3 hours after the LCT, systolic BP in the supine position decreased significantly in patients with OH (138.60 ± 16.51 vs 121.13 ± 16.59, $P = .018$), as shown in Figure 1.

3.3. Risk factor analysis of patients with LCT-induced OH

Univariate analysis revealed that patients with LCT-induced OH were significantly older (65.31 ± 4.17 vs 59.74 ± 5.55, $P = .019$) and had lower MoCA scores (17.5 [14, 27] vs 24 [14, 30], $P = .008$) than patients without OH. They also received a higher dose of L-dopa/benserazide than patients without OH (375 [250, 500] vs 250 [125, 500], $P = .022$), as shown in Table 2.

The results of multivariate logistic regression analysis demonstrated that older age was an independent risk factor for LCT-induced OH (odds ratio = 1.451; 95% confidence interval, 1.055–1.995; $P = .022$), as listed in Table 3.

4. Discussion

The dose of the LCT is 1.2 to 1.5 times the equivalent dose of L-dopa for all the anti-PD drugs that patients routinely take in the morning.[22] Thus, the LCT is a window for the observation of the side effects of short-term medication in patients with PD. As the disease progresses, an increase in the dose and frequency of L-dopa is inevitable. Thus, the LCT was beneficial in examining the short term effect of L-dopa increment on BP in our study. To better understand LCT-induced OH, in our study, patients with PD who had previously been diagnosed with OH were excluded. Eight patients with significant clinical symptoms were found to have OH at 2 hours after the LCT. Thus, the frequency of OH caused by the LCT was 10.3%. They used a median dose of 375 mg L-dopa/benserazide, and one of them still had OH 1 hour later even in the absence of any symptom. Compared with patients without OH, patients with LCT-induced OH expressed lower standing 1-minute BP and standing 3-minutes systolic BP at baseline and 2 hours following the administration of L-dopa/benserazide tablets. Moreover, the reduction in systolic BP in the supine position in patients with OH lasted for 3 hours in the LCT. These results clearly reflect the risks of the LCT and suggest that patients with low BP in the baseline standing position are likely to experience OH with increased L-dopa levels. Therefore, the safety of the LCT warrants further attention, and BP monitoring is recommended before and 2 to 3 hours after the LCT.

A previous single-dose response study reported that the incidence of L-dopa induced OH was 16.3% and found that low baseline BP, wearing-off, and concomitant use of MAO-B inhibitor or pramipexole were contributing factors related to OH.[24] Another study monitored BP in patients (mean age = 65.2 years) with early stage PD using a standardized standing test and reported that 73.1% of patients experienced L-dopa induced hypotension during the LCT, and the prevalence of OH in the

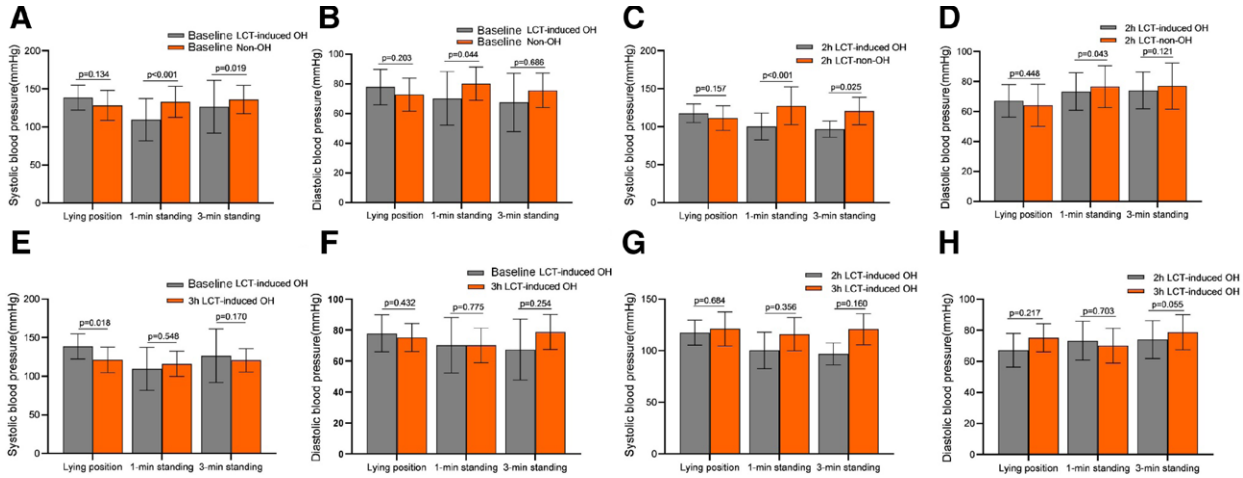

Figure 1. Blood pressure comparison between patients with and without orthostatic hypotension induced by the levodopa challenge test. BP = blood pressure, DBP = diastolic blood pressure, OH = orthostatic hypotension, SBP = systolic blood pressure.

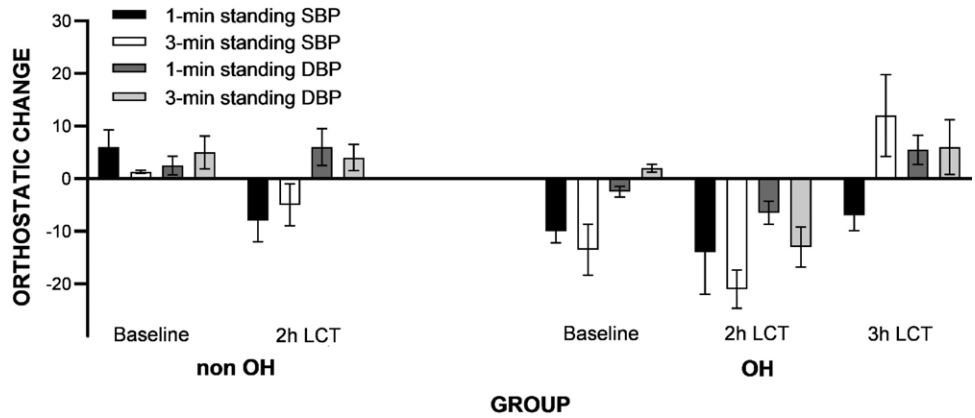

Figure 2. Orthostatic change in BP between patients with and without orthostatic hypotension induced by the levodopa challenge test. BP = blood pressure, DBP = diastolic blood pressure, OH = orthostatic hypotension, SBP = systolic blood pressure.

best "on-state" was 13.5%, while age was not associated with L-dopa related OH.[9] In the LCT, our patients with OH were all symptomatic, caomparatively older (mean age = 65.31 years), had lower MoCA scores, and took higher doses of L-dopa than patients without OH. Finally, multivariate logistic regression analysis confirmed that only age was an independent risk factor for LCT-induced OH. We speculated that the reason for the discrepancy in results might be that none of the participants in our study presented with OH at baseline.

A previous study reported that "older" patients (>70 years) should use lower doses of L-dopa than "younger" patients (≤70 years), especially patients over 70 years of age with a history of previous myocardial infarction.[25] Another study observing the safety of L-dopa therapy in 51 patients with idiopathic PD found that 83% of patients aged > 70 years had to stop L-dopa administration due to its BP-lowering effect.[26] Our study suggests that even short-lived tests, such as a median dose of 300/75 mg L-dopa/benserazide, may increase the risk of OH in patients with PD when performing LCT and can cause functional impairment in older patients. As both PD and aging are risk factors for OH, there is a high possibility that OH in older patients may be due to the use of anti-PD drugs.

The mechanism by which OH is induced by L-dopa remains unclear. An early clinical trial reported that 100-mg L-dopa could induce a mean 19.3-mm Hg reduction in systolic BP in older patients.[27] This reduction may be due to the action of dopamine on the adrenergic nerve endings or to the central nervous system. L-dopa has been suggested to interfere with BP by affecting aortic stiffness, arterial pressure, and cardiac contractility[28,29]; L-dopa was initially recognized as a causative or aggravating factor for OH. However, it was later argued that L-dopa therapy was not related to OH, but instead it induced cardiac protective effects by increasing HSP27 activity.[30] Noack et al[31] performed continuous noninvasive cardiovascular and ventilatory monitoring in patients with moderate PD to quantify the hypotensive effect of L-dopa. The results showed that the hypotensive response to L-dopa was mainly caused by a negative inotropic mechanism, rather than a peripheral diastolic mechanism. Barbeau et al[32] speculated that the effect of L-dopa on renin is a possible factor that leads to the exacerbation of OH in parkinsonism.

This study has some limitations. First, it had a relatively small sample size, thereby reducing the generalizability of our results. Second, this was a single-center study, and the patients were not followed up. Thus, it is necessary to conduct a prospective multicenter cohort study with more patients with PD, over a longer duration, to confirm our conclusions. Third, this study did not observe the relationship between different doses of L-dopa and BP changes at multiple time points during the LCT. Doing this may provide greater insight and will likely be more helpful in demonstrating BP trajectories. Lastly, for safety reasons, this study did not include patients who were still on antihypertensive drugs, even though it is common for patients to take L-dopa along with antihypertensive drugs at home or at hospital.

Table 2

Comparison of the clinical features between patients with and without orthostatic hypotension induced by the levodopa challenge test.

Indicators	LCT-induced OH group (n = 8)	Non-OH group (n = 70)	Z/*T* value	*P* value
Sex, n (%)				
Male	5 (62.5)	41 (58.6)	0.051	.822
Female	3 (37.5)	29 (41.4)		
Hypertension				
Present	3 (37.5)	27 (38.6)	0.127	.721
Absent	5 (62.5)	43 (61.4)		
PIGD dominant	6 (75)	37 (52.9)	0.371	.543
H–Y stage				
Early	3 (37.5)	30 (42.9)	0.382	.537
Middle	2 (25)	18 (25.7)		
Late	3 (37.5)	22 (31.4)		
Age (yr)	65.31 ± 4.17	59.74 ± 5.55	2.348	.019
Course of the disease	7 (3, 10)	5 (1, 11)	0.968	.333
Antihypertensive drugs (n, %)	3 (37.5)	17 (24.3)	−1.616	.106
Dopamine agonist (n, %)	3 (37.5)	26 (37.1)	−1.190	.234
Dopamine preparation (n, %)	7 (87.5)	61 (87.1)	−1.523	.128
Amantadine (n, %)	2 (33.3)	26 (37.1)	−1.469	.142
MAO-B inhibitor (n, %)	1 (12.5)	8 (11.4)	−1.696	.090
COMT inhibitor (n, %)	1 (12.5)	4 (5.7)	−0.884	.377
HAMA score	14 (7, 21)	11 (4, 25)	1.958	.050
HAMD score	9.5 (3, 19)	5 (2, 38)	1.708	.088
PDQ-39 score	31 (15, 117)	24 (2, 98)	1.102	.270
NMSQ score	10.33 ± 4.17	7.92 ± 3.86	−0.511	.396
PDSS score	13.5 (2, 28)	9 (0, 41)	−1.125	.261
MoCA score	17.5 (14, 27)	24 (14, 30)	−2.647	.008
LEDD (mg)	535 (238, 725)	496 (250, 800)	−1.705	.088
Maximum-improvement rate (%)	30 (20, 100)	50 (30, 90)	−1.376	.169
Levodopa/benserazide dose (mg)	375 (250, 500)	250 (125, 500)	−2.183	.022
UPDRS-II score	15.29 ± 2.50	13.00 ± 4.50	2.991	.224
UPDRS-III score (Baseline)	39.50 ± 16.39	34.91 ± 14.02	1.503	.139
UPDRS-III score (2 h LCT)	26.50 ± 10.39	21.91 ± 9.02	2.543	.280

COMT = catechol-o-methyltransferase, HAMA = Hamilton Anxiety Scale, HAMD = Hamilton Depression Scale, H–Y = Hoehn–Yahr, LCT = levodopa challenge test, LEDD = L-dopa equivalent daily dose, MAO-B = monoamine oxidase B, MoCA = Montreal Cognitive Assessment-Beijing version, NMSQ = Non-Motor Symptoms Questionnaire, OH = orthostatic hypertension, PDQ-39 = 39-item Parkinson's Disease Questionnaire, PDSS = Parkinson's Disease Sleep Scale, PIGD = postural instability and gait disorders, UPDRS = Unified Parkinson's Disease Rating Scale.

Table 3

Analysis of the influencing factors of orthostatic hypertension induced by the levodopa challenge test.

Indicators	Beta	Wald	OR	95% CI	*P* value
Age (yr)	0.372	5.250	1.451	1.055, 1.995	.022
MoCA score	0.325	0.151	0.723	0.140, 3.720	.698
Levodopa/benserazide dose	0.899	3.371	0.407	0.156, 1.063	.066
Baseline 1 min standing systolic blood pressure	0.260	3.590	0.771	0.590, 1.009	.058
Baseline 1 min standing diastolic blood pressure	0.268	0.569	0.765	0.381, 1.536	.451
Baseline 3 min standing systolic blood pressure	0.326	0.832	1.386	0.687, 2.796	.362

CI = confidence interval, MoCA = Montreal Cognitive Assessment-Beijing version, OR = odds ratio.

The fact that L-dopa can cause OH may be of concern to some clinicians, but the effect of acute L-dopa up-titration-induced OH in patients with PD during LCT has received very little attention. This study makes a unique contribution to the literature by questioning the safety of LCT. Our study shows that LCT can increase the risk of OH in patients without OH with PD and cause symptomatic OH in older patients (mean = 65.3 years). We emphasize the relevance of monitoring BP, especially before and 2 hours after receiving anti-PD drugs, in the daily management of older patients with parkinsonism.

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