

อิทธิพลของยารักษาโรคพาร์กินสันต่อความมั่นคงในการยืนทรงตัวแบบอยู่นิ่ง

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาผลยาโดปามีน (ยา Levodopa) ต่อความมั่นคงในการยืนทรงตัวขณะยืนแบบอยู่นิ่งในผู้ป่วยโรคพาร์กินสัน

วิธีวิจัย: ผู้ป่วยโรคพาร์กินสันจำนวน 27 คน เข้าร่วมการวิจัย ผู้ป่วยโรคพาร์กินสันได้รับการวัดความมั่นคงในการทรงตัวขณะยืนแบบอยู่นิ่ง ด้วยโปรแกรม Sensory Organization Test (SOT) ขณะก่อนและหลังได้รับยา Levodopa ในวันเดียวกัน ตัวแปรที่วัดด้วย SOT คือ ความเร็วของการเซ, เปอร์เซ็นต์ความมั่นคงสูงสุดในการยืนนิ่ง และเปอร์เซ็นต์การเคลื่อนข้อเท้า

ผลการศึกษา : ยา Levodopa เพิ่มความเร็วของการเซอย่างมีนัยสำคัญทางสถิติ ในภาวะไม่ใช้ข้อมูลจากการมองเห็น และภาวะที่มีการรบกวนข้อมูลจากการมองเห็น (อาศัยข้อมูลการรับรู้ผ่านข้อต่อ $P < 0.05$) เปอร์เซ็นต์การเคลื่อนข้อเท้าลดลงหลังจากได้รับยา เมื่อทดสอบในภาวะเปิดตาและปิดตา ($P < 0.05$) เมื่อเปรียบเทียบความมั่นคงสูงสุดในการยืนนิ่ง ขณะก่อนและหลังได้รับยาไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ

สรุปผล: ยา levodopa เพิ่มความสามารถในการรักษาสมดุลความมั่นคงในทรงตัวขณะยืนนิ่งภาวะรบกวนข้อมูลการรับรู้ผ่านข้อต่อและพึ่งพาข้อมูลจากการมองเห็นร่วมกับเลือกใช้ข้อสะโพกแทนข้อเท้า แต่ไม่มีผลต่อความสามารถในการรักษาสมดุลจุดศูนย์ถ่วงของร่างกายบนพื้นที่สัมผัสในขณะยืนแบบอยู่นิ่ง การศึกษานี้แสดงให้เห็นว่าความมั่นคงในการทรงตัวในผู้ป่วยพาร์กินสันต่างกัน ผลการศึกษานี้สามารถเป็นความรู้พื้นฐาน ซึ่งช่วยให้ผู้ให้การบำบัดตรวจประเมินและวางแผนแนวทางการรักษาสำหรับผู้ป่วยโรคพาร์กินสันได้

คำสำคัญ: Postural instability, Parkinson's disease, Sensory Organization Test (SOT), Levodopa, Balance

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Influence of Levodopa therapy on static balance in Parkinson's disease

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Abstract

Objective: To study the effect Levodopa on static standing balance in persons with Parkinson's disease (PD).

Methods: Twenty-seven persons with PD participated in the study. Persons with PD were tested for balance in a standing position using Sensory Organization Test (SOT) before ('off') and after taking the levodopa ('on') on the same day. SOT variables were average sway velocity, percentage of maximum stability and percentage of ankle strategy.

Results: Levodopa significantly increased sway velocity under visual absence and visual distorted conditions (somatosensory, $P < 0.05$). Percentage of ankle strategy decreased after the medication when testing under eye open and eye close conditions ($P < 0.05$). No significant differences were found when compared the maximum stability the standing balance between 'off' and 'on' medications.

Conclusion: Levodopa therapy improved the ability to maintain static balance under inappropriate somatosensory information and dependence on visual information with using hip strategy instead of ankle strategy but failed to influence the ability to maintain COG stability over the base of support in static standing. This study demonstrated that the different postural stability in PD. It could be fundamental data in helping clinicians to assess and plan an effective training regimen for PD.

Keywords: Postural instability, Parkinson's disease, Sensory Organization Test (SOT), Levodopa, Balance

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Introduction

A human body requires a balance or postural control system to stabilize the body⁽¹⁾. Postural control is defined as the act of maintaining, achieving or restoring the center of body mass within the base of support^(2,3) and as the ability to control the body position in space⁽⁴⁾. Postural stability is defined as an inherent of a person to maintain, achieve or restore a specific stage of balance and not to fall⁽³⁾. The inherent ability includes motor and sensory systems as well as the physical properties of the person in maintaining stability^(3, 5). Postural instability is one of the common problems in persons with Parkinson's disease (PD) and contributes to increased risk of falls, injuries, and limitation of daily activities^(6, 7).

Dopamine- replacement therapy (levodopa) is a main medication to relieve motor symptoms of PD. Levodopa has a marked symptomatic effect on cardinal signs of PD including rigidity, bradykinesia, and tremor. Efficacy of levodopa treatment on postural instability remains controversial. Laboratory assessments have provided insight that balance impairment responded poorly to dopaminergic medications⁽⁶⁻⁹⁾. Horak et al. reported that levodopa improved tonic background of postural muscular tone; however, it weakened the autonomic postural response to backward perturbations with decrease in the torque of agonist postural muscles⁽⁷⁾. Franks et al. reported the positive effect of dopaminergic therapy on the control of force and sequencing of centrally initiated postural preparations and postural tones on leg movement while rising onto the toes⁽⁶⁾. Most studies examined postural control and levodopa effect in dynamic balance condition. It remains unclear how the levodopa influence the postural instability in a static standing in PD.

Adequate balance control requires that a person is able to remain still or moves as they wish within any environment⁽⁵⁾. It also requires the ability to automatically respond to external perturbations, and the

effective strategies to do so⁽¹⁰⁾. Balance and postural control are complex responses that require several feed forward mechanisms including proprioceptive, visual and vestibular inputs⁽¹¹⁾. Quantitative measure of balance using a computerized posturography can isolate these inputs during an upright standing.

Assessment of balance in upright stance is an essential element for rehabilitation in persons with PD. Upright balance is required in performing everyday tasks such as standing, walking, turning, reaching and standing up from sitting. This study was to investigate the effect of levodopa on standing balance in persons with PD using the SOT of the computerized posturography. Sensory organization is the ability of an individual to effectively process each sensory system input to maintain balance. This can be done by suppressing inaccurate sensory system inputs while selecting appropriately from others, more accurate sensory cues to generate appropriate motor and postural responses. Sensory organization test (SOT) is the test for evaluating the ability of a person to effectively use visual, somatosensory and vestibular inputs to maintain postural stability and to select the input providing the most functionally appropriate information under a variety of conditions⁽¹²⁾.

The results of this study could provide quantitative information on static standing balance and the effect of levodopa medication in persons with PD for assessment, treatment planning and appropriate rehabilitation to improved stability in this population.

Methods

Subjects:

Twenty seven subjects with PD participated in the study. All subjects were voluntarily recruited from the Movement Disorder Clinic, Siriraj Hospital, Mahidol University, Bangkok. The inclusion criteria for all subjects were 1) no musculoskeletal problems leading to functional limitation of lower extremities

and pain that could affect balance while being tested, 2) ability to understand and follow simple instructions, and 3) no alcohol consumption within 24 hours prior to testing. Inclusion for PD subjects were 1) diagnosis of PD by neurologists and response to levodopa therapy, 2) PD within stage I-III of the Hoehn and Yahr Disability Scales ⁽¹³⁾, 3) receiving levodopa therapy and were medically stable. Exclusion criteria for all subjects were 1) persistence of vertigo symptoms, defined as the feeling of everything turning and inability to keep balance and 2) a history of peripheral neuropathy.

Assessment

The Smart Posturography Master® system (version 5, Neurocom International, Inc, Clackamas, OR) was used to evaluation of Sensory organization test (SOT). SOT was used to quantify the static balance in standing position to ability to use and integrate vision, somatosensory and vestibular inputs effectively to maintain balance with minimal sway.

SOT consists of six conditions. Condition 1: eyes open, fixed visual surround and fixed support surface (EO). Condition 2: eyes close and fixed support surface (EC). Condition 3, eyes open, fixed support surface and sway visual surround (SVEO). Condition 4: eyes open, fixed visual surround, and sway support surface (SSEO). Condition 5: eyes close and sway support surface (SSEC). Condition 6: eyes open, sway visual surround and sway support surface (SSSV) ^(12, 14). In the conditions 1, 2 and 3, the subject being tested mainly used somatosensory sensation (i.e. skin, joints, muscles) to control balance. In condition 4, the subject mainly used vision, and in condition 5 and 6, the subject mainly uses vestibular to control balance.

Three variables produced from the SOT were studied: 1) average sway velocity (degrees/sec) indicated the ability to maintain COG stability in perimeter of limit of stability (LOS) using the ankle joint. The greater value indicates lesser the stability of the person;

2) percentage of maximum stability indicated center of gravity stability. The percentage ranges from 0 (i.e. fall) to 100 (maximal stability). The higher percentage indicates the better stability of the person and 3) percentage of ankle strategy indicated the extent the person used the ankle joint in balance control. The higher value indicates the more ankle joint used to maintain balance which reflects a better stability.

During the test, the subjects were asked to maintain upright stance for 20 seconds, on a movable platform with as little sway as possible with a minute rest between trails. This duration is optimum for postural stability measurements ⁽¹⁵⁾.

Procedure:

All subjects signed a consent form approved by the Ethical Committee on Research Involving Human Subject, Siriraj Hospital, Mahidol University, Bangkok. Subjects were rated according to the Hoehn and Yahr Disability Scales and the Unified Parkinson's Disease Rating Scale ⁽¹³⁾. A brief medical history, demographic information, and duration of the disease were obtained from subjects' reports and/or their medical records.

All clinical evaluation and balance testing were performed while the subjects were 'off' (~12-hours withdrawal of levodopa) and then 'on' (~ 45 minutes after taking the medication). Stage 'on' medication was determined by an observation of parkinsonian signs, an improved rate of finger and/or foot tapping on the Unified Parkinson's Disease Rating Scales (UPDRS) ⁽⁷⁾. For 'off' medication testing, the subjects were instructed to take the last dose of their medications the night before the testing date and come to the laboratory the following morning without taking any antiparkinsonian medications. Subjects were practiced to be familiarized with the task before testing.

After completing all clinical evaluation and the SOT test, the subjects were allowed to take their medications immediately and were asked to wait ap-

proximately 45 minutes or more for 'on' medication assessment. The UPDRS were rated again for 'on' medication state by the same neurologist who rated the 'off' state. The test procedures were repeated in the same manner as the 'off' medication test. Total time for all tests was approximately 75 minutes (total time is off, on medication and rest) for each subject.

Statistical Analysis

The statistical analyses of the data were performed by using SPSS for Microsoft Windows Release version 18. Means and standard deviations of demographic data were descriptively summarized. Paired t-tests were used to compare between the two medication states. The level of statistical significance was set at the 0.05 level.

Results

Characteristics of subjects are displayed in the **Table 1**. There were two right hemiparkinsonism and seven left hemiparkinsonism subjects. One subject needed a cane for ambulation; others were able to walk independently without any assistive device. Six subjects had dyskinesia during 'on' medication. All subjects were able to complete the test without external assistance.

Table 1 Subject characteristics

Characteristics	Mean $\pm$ SD
Age (yrs)	65.0 $\pm$ 9.00
Male	65.92 $\pm$ 11.20
Female	64.12 $\pm$ 6.68
BMI ^a (kg/m ²)	23.42 $\pm$ 4.12
HY	2.0 $\pm$ 0.83
Year of PD	5.33 $\pm$ 4.21
UPDRS ^b (off)	20.48 $\pm$ 11.19
UPDRS (on)	9.48 $\pm$ 6.61

^aBMI = Body Mass Index

^bUPDRS = Unified Parkinson's Disease Rating Scales

Average sway velocity in the following testing conditions improved after the administration of levodopa; EO (0.26 $\pm$ 0.16 vs. 0.39 $\pm$ 0.24 degrees/s, $P=.001$), EC (0.38 $\pm$ 0.16 vs. 0.55 $\pm$ 0.39 degrees/s, $P=.009$), SVEO (0.36 $\pm$ 0.185 vs. 0.55 $\pm$ 0.37 degrees/s, $P=.011$), SSEC (1.18 $\pm$ 0.48 vs. 1.38 $\pm$ 0.7 degrees/s, $P=.042$) (**Table 2**). No significant differences were found on the average sway velocity under the SSEO and SSSV conditions after the levodopa administration (Table 2). No significant differences were also found in percentage of maximum stability (**Table 3**). Levodopa decreased percentage of ankle strategy in EO (96.4 $\pm$ 0.97 vs. 95.6 $\pm$ 1.57, $P=.028$) and EC (94.5 $\pm$ 2.68 vs. 92.3 $\pm$ 3.46, $P=.023$) conditions (**Table 4**).

Table 2 Effect of Levodopa therapy on average sway velocity (N = 27)

SOT condition	OFF	ON	t	P - value
	Mean $\pm$ SD (degree/sec)	Mean $\pm$ SD (degree/sec)		
EO	0.26 $\pm$ 0.16	0.39 $\pm$ 0.24	-3.748	0.001 *
EC	0.38 $\pm$ 0.16	0.55 $\pm$ 0.39	-2.812	0.009 *
SVEO	0.36 $\pm$ 0.185	0.55 $\pm$ 0.37	-2.744	0.011 *
SSEO	0.62 $\pm$ 0.29	0.78 $\pm$ 0.43	-1.912	0.067
SSEC	1.18 $\pm$ 0.48	1.38 $\pm$ 0.70	-2.142	0.042 *
SSSV	1.15 $\pm$ 0.58	1.30 $\pm$ 0.49	-1.264	0.217

* $P < 0.05$

SOT= Sensory Organization Test, EO = eyes open with fixed support; EC = eyes close with fixed support;

SVEO = sway reference vision with eyes open; SSEO = sway reference support with eyes open;

SSEC = sway reference support with eye close; SSSV = sway reference vision and support

Table 3 Effect of Levodopa therapy on percentage of maximum velocity (N = 27)

SOT condition	OFF (N=27)	ON (N=27)	t	P - value
	Mean $\pm$ SD (%)	Mean $\pm$ SD (%)		
EO	92.9 $\pm$ 4.63	92.7 $\pm$ 4.1	0.186	0.845
EC	89.3 $\pm$ 5.12	87.4 $\pm$ 9.78	1.198	0.242
SVEO	87.4 $\pm$ 9.87	87.4 $\pm$ 6.97	0.018	0.986
SSEO	74.9 $\pm$ 11.40	72.4 $\pm$ 13.87	0.894	0.379
SSEC	52.0 $\pm$ 23.64	53.1 $\pm$ 17.19	-0.265	0.793
SSSV	48.1 $\pm$ 24.99	45.7 $\pm$ 14.72	0.572	0.572

SOT= Sensory Organization Test, EO = eyes open with fixed support; EC = eyes close with fixed support;

SVEO = sway reference vision with eyes open; SSEO = sway reference support with eyes open;

SSEC = sway reference support with eye close; SSSV = sway reference vision and support

Table 4 Effect of Levodopa therapy on percentage of ankle strategy (N = 27)

SOT condition	OFF	ON	t	P - value
	Mean $\pm$ SD (%)	Mean $\pm$ SD (%)		
EO	96.4 $\pm$ 0.97	95.6 $\pm$ 1.57	0.894	0.028 *
EC	94.5 $\pm$ 2.68	92.3 $\pm$ 3.46	1.772	0.023 *
SVEO	93.7 $\pm$ 3.79	92.7 $\pm$ 5.36	1.074	0.293
SSEO	83.4 $\pm$ 6.94	82.3 $\pm$ 11.37	0.622	0.539
SSEC	70.9 $\pm$ 14.84	72.5 $\pm$ 16.08	-0.741	0.465
SSSV	67.2 $\pm$ 22.55	67.9 $\pm$ 19.61	0.891	-0.139

SOT= Sensory Organization Test, EO = eyes open with fixed support; EC = eyes close with fixed support;

SVEO = sway reference vision with eyes open; SSEO = sway reference support with eyes open;

SSEC = sway reference support with eye close; SSSV = sway reference vision and support

Discussion

Our results demonstrated that levodopa increased ankle sway velocity in several static balance testing conditions including condition 1 (eye open, EO), condition 2 (eye close, EC), and condition 3 (sway visual surround, SVEO). These were the testing conditions that the subjects mainly use somatosensory sensation to control their balance. In testing condition 2 and 3, visual enclosure and misleading visual input, respectively, were provided with respect to the vertical orientation. When these sensory inputs are not available or provide misleading information concerning body orientation, the somatosensory system has main influence on balance control. Increased sway velocity from the levodopa supported the previous findings that the control of force and sequence of the centrally initiated postural preparations and postural tone as well as postural adjustment appeared to involve dopaminergic circuits⁽⁶⁻⁹⁾.

Levodopa also increased sway velocity in the testing condition 5, which was mainly dependent on vestibular system for balance control due to absence of visual input together with an inaccurate somatosensory input. This finding might imply an influence of levodopa on vestibular system. The role of levodopa on vestibular

system required further study. A previous study reported that vestibular system was intact in persons with PD⁽¹⁶⁾. However, vestibular system dysfunction in PD was not clearly understood, and not widely studied.

Our results demonstrated that levodopa decreased percentage of ankle strategy in testing condition 1 (eye open, EO) and 2 (eye close, EC). The changes were in agreement of the increased sway velocity in these two conditions by levodopa. The velocity increased, so the persons with PD decreased the use of ankle strategy to control balance, and possibly increased the use of hip strategy to control balance. This purposed that an increased in postural sway after the intake of dopaminergic drugs plausibly as a result of the decreased rigidity and related difference in the strategy of balance⁽¹⁷⁾. Moreover, there was a reduction in use of ankle strategy but more increase in use of hip strategy could be due to muscle weakness in flexor, extensor and trunk muscles together with aging process. These may lead to use hip strategy and development of a stooped posture by keeping COG from perimeter close to center and prevent falls in this task⁽¹⁸⁾.

Levodopa did not have influence on overall maximum stability. This finding was in agreement with

other previous studies that dopaminergic medication did not change static balance⁽⁷⁾, even though the medication increased sway velocity. The increased sway velocity did not change the maximum stability. Levodopa was observed as paradoxical effects. Several aspects of autonomic postural responses were unchanged or deviated from normal with administration of levodopa, even though the same patients clearly improved their clinical motor behavior with the influence of levodopa. Dysfunction in nondopaminergic pathways may explain why this medication did not improved some aspects of postural control⁽⁷⁾.

In over all, our results supported that statement that levodopa did not improve static balance in standing. Literatures have demonstrated that dopamine replacement therapy substantially improved clinical disability and specific motor tasks without improving balance⁽⁶⁻⁹⁾. A possible explanation for this discrepancy, BG has complex circuitry that regulates the various types of postural control and motor behaviors by separate neural circuits. As a consequence, the control of force and sequencing of centrally initiated postural preparations and postural tones appear to involve dopamine circuits^(6,7). In contrast, the control of force of peripherally triggered postural reactions and ability to use central set appear to involve nondopaminergic circuits⁽⁷⁻⁹⁾. Therefore, it seems possible that the balance impairment in PD is related to a combination of both dopaminergic and nondopaminergic lesion⁽⁸⁾ or it may be due to fundamental changes in the organization of the basal ganglia- thalamo-cortical circuit⁽¹⁷⁾.

Balance in the standing position is categorized into static and dynamic. The term static balance refers to an individual's stationary position in quiet upright stance and ability to keep the center of mass within stability limits⁽¹⁹⁾. In contrast, the dynamic balance is the ability to maintain balance during movement and during locomotion with weight shift where the base of support of the body is not moving^(20, 21). The ability to maintain the center of gravity (COG) during movement

within limit of stability is fundamental to the successful performance of daily activities^(19,22,23). Persons with PD are likely to lose this control due to an inability to adequately balance the COG of the body over the base of support⁽⁶⁾, especially when responding to an external, unexpected perturbation^(6,7,9,24).

It was proposed that the role of basal ganglia (BG) in the integration of proprioceptive signals with visual information was essential in guiding movement⁽²⁵⁾. Based on anatomical evidence, BG played a critical role in detecting the context of cortical activation and responded by choosing the appropriate sets of motor control from associate sensory cues for automatically learned movements as well as reinforce patterns of cortical activity during movement preparation and excursion⁽²⁶⁾. BG receives somatotopically organized input from somatosensory area and nearly cortical regions⁽²⁷⁾ and several somatosensory centers integrate this information to automatically regulate contraction of postural muscles in order to maintain balance⁽¹⁹⁾.

This implied that the PD patients decrease in the ability to maintain static balance under inappropriate somatosensory information and dependence on visual information after taking medication. Persons with PD increased dependence on visual cues when performing perceptual and motor tasks, which may reflected the adaptive strategy used by these patients to partly compensate for proprioceptive deficits⁽²⁸⁾. A few of study suggested that antiparkinsonian medications were associated with a modest acute suppression in central responsiveness to joint position^(18, 29). Our finding might imply that the dopaminergic medication influenced on cerebellar function for balance control. Several studies also proposed that persons with PD might use visuomotor pathways through cerebellar circuit bypassing the damaged basal ganglia⁽³⁰⁻³³⁾.

In contrast, several studies suggested that postural control system in PD appears to function appropriately in response to various combinations of

sensory deprivation or feedback, but the ability of the system to generate timely and accurately calibrated motor commands⁽³⁴⁾ or the ability to adapt quickly to the demands of an unfamiliar and challenging task⁽¹⁶⁾ may be impaired or an improvement of postural tone reflected by a reduction in rigidity and improvement in bradykinesia may increase average sway velocity^(7, 24).

Limitation and suggestion

In this study was a limited sample of PD patients, its relation with disease severity and progression. Stage I to III of severity of PD (mild to moderate) was only measured by SOT, but not advance PD stage (stage IV to V) who have predominantly postural instability. The further study should investigate characteristics of postural instability in each disease severity.

Conclusion and clinical implication

This study provided quantitative information on the effect of levodopa on postural stability in persons with PD during static balance in standing. Levodopa did not show all positive effect on postural stability. Somatosensory and visual information have impact on the parameters of postural stability and influence on antiparkinsonian medication in PD patients. Clinicians in rehabilitation should be aware of postural control in response to levodopa as paradoxical effect to provide suitable management to improve the impaired stability and prevent the loss of balance.

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