Orthostatic hypotension: a non-motor complication assessment in 82 patients with idiopathic Parkinson's disease in Phramongkutklao Hospital

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Objective: *Parkinson's disease (PD) is one of the neurogenic etiologies of orthostatic hypotension, a non-motor symptoms complex, that tends to be under-recognized and under-treated leading to a major cause of disability for PD patients. This complication is associated with one or recurrent falls causing mortality and morbidity. To the authors' knowledge, there is no study about this condition in Thai PD population. The authors therefore aimed to determine the frequency, clinical and risk factors of orthostatic hypotension in PD patients treated in Phramongkutklao Hospital.*

Material and Method: *The authors enrolled consecutive patients with idiopathic PD over a 10-month period. Supine and standing blood pressure (BP) were measured sequentially as the standard techniques. Orthostatic hypotension (OH) was diagnosed if there was a reduction in systolic or diastolic BP of at least 20 or 10 mmHg respectively within 3 minutes after standing. The authors analyzed for the frequency of this condition as well as determined the risk factors between the OH and non-OH groups.*

Results: *The number of patients enrolled was 82 with the mean age of 69 years. The median duration of PD was 4 years. Eighty-five percent were in Hoehn & Yahr stage 1-3. Thirty-three patients (40.2%) had orthostatic hypotension and 70% of them were asymptomatic. By univariate and multivariate analysis, the risk factors for this condition were the longer duration of PD diagnosis, the more advanced staging and the use of selegiline.*

Conclusions: *The frequency of orthostatic hypotension among the present PD was 40.2%. The longer duration of disease, the more advanced stage of Parkinson's disease and selegiline usage were the factors associated with this non-motor condition.*

Keywords: *Orthostatic hypotension, Parkinson's disease, Non-motor complication*

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Orthostatic hypotension is a common problem leading to significant morbidity and mortality[1]. It is associated with several conditions including an increased rate of falls, fractures, syncope, and a history of myocardial infarction or transient ischemic attack[2]. Orthostatic hypotension also may be a predictor of ischemic stroke and cognitive impairment in elderly people[3,4]. In community dwelling individuals over 65 years of age, its prevalence is approximately 20%; in those over 75 years of age, it is as high as 30%[1]. From a Thai community epidemiological study conducted in 334 elderly subjects, postural hypotension accounted for 11.3% in non-hypertensive subjects and 14.8% in hypertensive subjects[5].

Parkinson's disease (PD) is the most prevalent neurodegenerative disease after Alzheimer's disease. It is estimated that 1% of the population aged between 65-74 years are affected with PD[6]. Many data indicate that orthostatic hypotension may also be presented in Parkinson's disease (PD), not only in multiple system atrophy (MSA)[7-9]. PD, therefore, is recognized to be one of the neurogenic etiologies of orthostatic hypotension[10]. However, the clinical relevance of PD with orthostatic hypotension is poorly understood.

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Previous studies had suggested that 43-58.2% of both hospital-based and community-based PD patients had orthostatic hypotension[4,11-14]. Two conflicting studies had debated about orthostatic hypotension in terms of risk factor for falls in PD[12,13]. A cohort study demonstrated that individuals with orthostatic hypotension were older than those without it, but there was no difference in PD disease duration or severity between groups[11]. Another interesting study obtained from 51 newly diagnosed PD patients showed orthostatic hypotension of 14%[15]. Despite some data available from the Western countries, there is no information available in Thailand. To the authors' knowledge, there are very few publications conducted from Asian population[16]. The authors, therefore, would like to study this non-motor co-morbidity of PD from our tertiary medical centre. The aims of the present study were to determine the frequency, clinical features and risk factors of orthostatic hypotension in the presented patients diagnosed with idiopathic Parkinson's disease in Phramongkutklao Hospital.

Material and Method

The presented cross-sectional study was conducted in 2007. The authors enrolled 82 consecutive idiopathic Parkinson's disease patients diagnosed using United Kingdom Parkinson's Disease Society brain bank criteria[17] from the authors' Neurology out-patient clinic over a 10-month period (May 1st, 2007-February 28th, 2008). The authors included patients whose age was more than 45 years. Exclusion criteria were 1) secondary parkinsonism from drugs or metabolic diseases, 2) parkinson plus syndromes, and 3) peripheral neuropathy. The authors reviewed medical records and interviewed patients. Demographic data included age, sex, co-morbidities, and current medications. The falling and fainting experiences were also reviewed. PD severity was assessed by the Hoehn and Yahr scale[18].

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the brachial artery by using a standard sphygmomanometer in the supine recumbence for at least 5 minutes. Then, patients were measured again in the standing position within 3 minutes after changing the position. Orthostatic hypotension was diagnosed by the criteria of the joint consensus committee of the American Autonomic Society and the American Academy of Neurology, which defined orthostatic hypotension (OH) as a reduction in SBP of at least 20 mmHg, or DBP of at least 10 mmHg within three minutes of assuming an erect posture[8]. The authors then analyzed for the frequency of this condition as well as the risk factors by comparing demographic data and symptoms between the OH and non-OH groups. Also, the authors further divided the presented PD for subgroup analysis to find out more precise risk factors.

Statistical analysis

Data were presented as number, percent, mean and standard deviation. Median and inter-quartile range (IQR) were reported in some variables, in those which did not fit normal distribution. Qualitative variables were compared by using chi-square or Fisher's exact test. Quantitative data were analyzed by t-test and Mann-Whitney U test for parametric and non-parametric variables respectively. Univariate + Multirariate analysis were also calculated. P-value < 0.05 was considered as statistically significance. Statistical analysis was assessed by statistic program, SPSS version 11.5.

Results

Overall there were 82 idiopathic PD patients, [57 males (69.5%), and 25 females (30.5%)]. The average age was 69.2 years and ranged 45-88. The median duration of PD diagnosis was 4 years and IQR was 1.6-8.3. The most common comorbid condition in the present series was hypertension (47 cases, 57.3%). Thirty-seven of the hypertensive patients were prescribed antihypertensive medications in which diuretics were commenced in 8 cases. The demographic characteristics are shown in Table 1.

At the time of enrollment, all patients revealed tremor; approximately one third had bradykinesia and / or rigidity, while postural abnormality was detected in 21 cases (25.6%). Eighty-five percent were ambulatory and physically independent as Hoehn & Yahr staging was between 1 and 3 (Table 2). Most patients were prescribed levodopa (L-dopa), which mean daily dosage was approximately 500 mg and the maximum dosage was 1,300 mg/day. Polytherapy was commenced in 58.5% including one or more of the following medications: dopamine agonists or selegiline, catechol-o-methyl transferase (COMT) inhibitor, or anticholinergic drugs which were added on to L-dopa. The PD severity rating and treatment are highlighted in Table 2.

Thirty-three patients (40.2%) were diagnosed with orthostatic hypotension. Only 10 cases (30.3%) were symptomatic orthostatic hypotension, and had experience of a fall. On the contrary, most orthostatic

Table 1. Demographic data of the enrolled subjects

Variables	Overall (n = 82) n (%)	Orthostatic hypotension (n = 33) n (%)	Non- orthostatic hypotension (n = 49) n (%)	p-value
Sex				
Male	57 (69.5)	25 (75.8)	32 (65.3)	0.313
Female	25 (30.5)	8 (24.2)	17 (34.7)	-
Age (year) mean ± SD	69.2 ± 10.3	71.3 ± 11.0	67.7 ± 9.7	0.118
Underlying disease				
Hypertension	47 (57.3)	22 (66.7)	25 (51.0)	0.160
Ischemic heart disease	13 (15.9)	7 (21.2)	6 (12.2)	0.276
Dementia	14 (17.1)	4 (12.1)	10 (20.4)	0.328
Previous stroke	10 (12.2)	6 (18.2)	4 (8.2)	0.174
Diabetes mellitus	12 (14.6)	4 (12.1)	8 (16.3)	0.597
Non-PD current medications				
Antihypertensive	37 (45.1)	15 (45.5)	22 (44.9)	0.960
Diuretics	8 (9.8)	4 (12.1)	4 (8.2)	0.554
Antidepressant	15 (18.3)	5 (15.2)	10 (20.4)	0.546
AchE inhibitor (for dementia)	13 (15.9)	4 (12.1)	9 (18.4)	0.448
Antipsychotic	10 (12.2)	5 (15.2)	5 (10.2)	0.502

PD: Parkinson's disease, AchE: acetyl cholinesterase

Table 2. The characteristics of Parkinson's disease in the enrolled subjects

Variables	Overall (n = 82) n (%)	Orthostatic hypotension (n = 33) n (%)	Non- orthostatic hypotension (n = 49) n (%)	p-value
PD Staging (Hoehn & Yahn)				
I	24 (29.3)	6 (18.2)	18 (36.7)	
II	21 (25.6)	7 (21.2)	14 (28.6)	
III	25 (30.5)	11 (33.3)	14 (28.6)	0.003*, 0.006**
IV	9 (11.0)	7 (21.2)	2 (4.1)	
V	3 (3.7)	2 (6.1)	1 (2.0)	
PD Duration, median (IQR); (years)	4.0, (1.6-8.3)	6.0, (3-9.5)	3.0, (1-8)	0.023*, 0.024**
Falling experience	21 (25.6)	10 (30.3)	11 (22.4)	0.424
Current PD medications				
Levodopa	78 (95.1)	32 (97.0)	46 (93.9)	0.524
Daily dosage (mg) mean ± SD	454 ± 250.8	482.8 ± 276.4	434 ± 232.4	0.438
Dopamine agonist	29 (35.4)	10 (30.3)	19 (38.8)	0.431
COMT inhibitor	27 (32.9)	11 (33.3)	16 (32.7)	0.949
Trihexyphenidyl (artane)	12 (14.6)	6 (18.2)	6 (12.2)	0.456
Selegiline	8 (9.8)	6 (18.2)	2 (4.1)	0.035*, 0.006**

Note: * $p < 0.05$ by univariate analysis, ** p value by multivariate analysis
COMT: Catechol-O-methyl transferase, IQR: interquartile range,

Table 3. Blood pressure measurement of the patients with and without orthostatic hypotension

Group	Supine mean ± SD	range	Standing mean ± SD	range
Overall (n = 82)				
SBP (mmHg)	143.3 ± 22.4	98-201	136.5 ± 24.8	72-202
DBP (mmHg)	78.3 ± 12.9	50-111	77.9 ± 13.5	48-111
Pulse rate (/min)	72.1 ± 13.6	40-107	76.3 ± 15.3	45-120
Orthostatic hypotension (n = 33)				
SBP (mmHg)	149 ± 24.3	120-201	123.5 ± 21.7	72-174
DBP (mmHg)	81.4 ± 13.9	56-111	73.2 ± 14.4	48-111
Pulse rate (/min)	75.8 ± 13.2	44-107	81.9 ± 17.1	46-120
Non- orthostatic hypotension (n = 49)				
SBP (mmHg)	139.5 ± 20.4	98-200	145.2 ± 23.1	85-202
DBP (mmHg)	76.2 ± 12.0	50-108	81.1 ± 12.1	50-106
Pulse rate (/min)	69.6 ± 13.5	40-102	72.5 ± 12.9	45-105

SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 4. The association between orthostatic hypotension among different groups of the patients with Parkinson's disease

Variables	Total (n = 82) n (%)	Orthostatic hypotension (n = 33) n (%)	Non-orthostatic hypotension (n = 49) n (%)	p-value
Age (years)				
≤60	15 (18.3)	6 (18.2)	9 (18.4)	0.983
>60	67 (81.7)	27 (81.8)	40 (81.6)	
PD status				
Unilateral disease	24 (29.3)	6 (18.2)	18 (36.7)	0.700
Bilateral disease	58 (70.7)	27 (81.8)	31 (63.3)	
Duration of disease (years)				
< 3	37 (45.1)	9 (27.2)	28 (57.2)	0.021*
3-6	20 (24.4)	12 (36.4)	8 (16.3)	
> 6	25 (30.5)	12 (36.4)	13 (26.5)	
Levodopa dosage (mg)				
≤500	51 (65.4)	21 (65.6)	30 (65.2)	0.97
> 500	27 (34.6)	11 (34.4)	16 (34.8)	
PD medication				
Monotherapy	34 (41.5)	13 (39.4)	21 (42.9)	0.755
Polytherapy	48 (58.5)	20 (60.6)	28 (57.1)	

hypotension patients (69.7%) were asymptomatic. Eleven patients (22.4%) in the non- orthostatic hypotension group also reported a falling experience. Fortunately, there were no fracture consequences occurring in all PD with falls. Blood pressure values during the supine recumbence and the standing position were highlighted in Table 3.

From the present study, the authors

demonstrated that the diagnostic duration of Parkinson's disease, more advanced staging and selegiline usage were significantly associated with orthostatic hypotension by univariate and multivariate analysis (Table 2). The orthostatic hypotension group had significantly longer median duration of PD diagnosis than the non-orthostatic hypotension group (6 years versus 3 years respectively), p-value 0.023, Table 2 and 4. Moreover, individuals prescribed selegiline were found more OH number than to those without this medication (18.2% versus 4.1% respectively), p 0.006. The authors further performed the subgroup analysis in the different age group (≤ 60, >60 years), PD characters (unilateral, bilateral involvement), L-dopa dose (≤ 500, > 500 mg/day) and PD specific medications (mono- or poly-therapy); however, the authors could not find a difference between these subgroups study (Table 4).

Discussion

The autonomic nervous system (ANS) plays an important role in maintaining blood pressure and perfusion when a person changes position[10]. The sympathetic nervous system adjusts the tone in arteries, veins, and the heart. Baroreceptors located primarily in the carotid arteries and aorta exquisitely sensitive to changes in blood pressure. When the baroreceptors sense a slight drop in pressure, a coordinated increase in sympathetic outflow occurs. Arteries constrict to increase peripheral resistance and blood pressure, heart rate and contractility increase. In general, all parts of the cardiovascular and nervous systems must work together. If there is impairment of the ANS, orthostatic hypotension may result[10].

Orthostatic hypotension (OH) is considered as an important clinical marker for the diagnosis of multiple system atrophy (MSA) and is incorporated in the main clinical criteria for the diagnosis of this condition[6-8]. In clinicopathological retrospective studies, early and severe orthostatic hypotension has been reported in patients who have been confirmed with MSA[19,20]. Parkinson's disease is identified by the disruption of dopaminergic neurotransmission in the basal ganglia. On pathological examination, dopaminergic neurons in substantia nigra are markedly reduced, and Lewy bodies (cytoplasmic inclusions) are presented in the residual dopaminergic neurons[21]. Results of neuropathological studies indicate that the ANS is also involved in PD. In fact, Lewy bodies also can be detected in both central and peripheral structures involved in ANS[22-25].

From the present study, PD characteristics were 1) average age more than 65 years, 2) male predominant, and 3) 85% in stage 1-3. The frequency of orthostatic hypotension in the presented PD individuals was 40.2%. Interestingly, most patients with this condition remained asymptomatic causing the under-recognition. This can be harmful for the falling and fracture consequences. Physicians therefore should consider and detect this condition by routine blood pressure measurement of the different positions as well as survey other ANS or non-motor dysfunctions such as sudo-motor, bowel and bladder functions. Additionally, patients with symptomatic orthostatic hypotension would have benefit from a stepped approach with initial non-pharmacologic and pharmacologic interventions. Either asymptomatic or symptomatic orthostatic hypotension, physicians should avoid prescribing the potentially hypotensive medications such as nitrates, tricyclic antidepressant, neuroleptics and alpha-blockers.

The frequency of orthostatic hypotension in the presented PD (40.2%) was not different from other Western countries, which ranged from 43 to 58%[4,11-14]. This frequency, nevertheless, was obviously higher than orthostatic hypotension among a Thai elderly community survey, which represented less than 15%[5]. This would emphasize to the authors that PD was an important cause of orthostatic hypotension in geriatrics. In the past, advanced age, PD stage and L-dopa treatment were widely assumed to be the risk factors of orthostatic hypotension in PD. From the present study, the duration of PD diagnosis, disease staging and selegiline used were risk factors of the postural hypotension which contrasted to the data from Japan that postulated a possible effect of L-dopa[16]. In the presented series, levodopa had been widely prescribed, in which more than 95% of the presented PD had been taking it, so the different percentage of this medication between OH and non-OH groups were negligible to be able to analyze the risk factor of this condition.

Conclusion

The frequency of orthostatic hypotension among the presented Parkinson's disease individuals was 40.2%. Approximately 70% of them were asymptomatic. This emphasizes to the authors that relatively minor degrees of orthostatic hypotension in PD are not rare. From the information available, the longer duration of Parkinson's disease, the more advanced PD stage and the use of selegiline were the risk factors of this condition in Parkinson's disease.

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ภาวะ orthostatic hypotension ภาวะแทรกซ้อนชนิด non-motor ศึกษาจากผู้ป่วย โรคพาร์คินสัน 82 ราย ในโรงพยาบาลพระมงกุฎเกล้า

พาสิริ สิทธินามสุวรรณ, ปฏิมา อรวรรณหโณทัย, กฤษฎา ไตรธรรม, เจษฎา อุดมมงฆล, ปานศิริ ไชยรังสฤษดิ์, โยธิน ชินวลัญช์, สามารถ นิธินันทน์, วรรณา วงศ์เมฆ, สีมา ศุภเกษม, จิตถนอม สุวรรณเตมีย์

ภูมิหลัง: *โรคพาร์คินสันเป็นสาเหตุหนึ่งของภาวะความดันตกจากการเปลี่ยนท่า (orthostatic hypotension) ซึ่งเป็นหนึ่งในภาวะแทรกซ้อนของโรคชนิด non-motor ที่มักได้รับการวินิจฉัยและรักษาค่อนข้างล่าช้า และมีความสัมพันธ์กับการล้มซึ่งมีผลต่อการตายและการพิการในผู้ป่วยสูงอายุที่เป็นโรคพาร์คินสัน เนื่องจากยังไม่มีรายงานการศึกษานี้ในประเทศไทยมาก่อน คณะผู้วิจัยจึงต้องการศึกษาหาความชุก อาการ และปัจจัยเสี่ยงของภาวะนี้ในผู้ป่วยพาร์คินสันที่รับการรักษาในร.พ.พระมงกุฎเกล้า*

วัสดุและวิธีการ: *ผู้วิจัยศึกษาผู้ป่วยโรคพาร์คินสัน ที่เข้ารับการรักษาแบบผู้ป่วยนอก ระยะเวลาทั้งสิ้น 10 เดือน ทำการวัดความดันโลหิตในท่านอนราบและยืนตามวิธีมาตรฐาน ถ้าพบความดันซิสโตลิกในท่ายืนลดลงจากท่านอน 20 มิลลิเมตรปรอท หรือความดันไดแอสโตลิกลดลง 10 มิลลิเมตรปรอท ภายใน 3 นาทีหลังจากยืน จะให้การวินิจฉัยว่ามีภาวะ orthostatic hypotension จากนั้นทำการวิเคราะห์ความชุกของโรค อาการ และหาปัจจัยเสี่ยงระหว่างกลุ่มที่มีความดันปกติและผิดปกติ*

ผลการศึกษา: *ผู้ป่วย 82 คน มีอายุเฉลี่ย 69 ปี เป็นโรคนานเฉลี่ย 4 ปี ผู้ป่วยร้อยละ 85 อยู่ในระยะ 1-3 ของ Hoehn & Yahr พบภาวะความดันต่ำหลังการเปลี่ยนท่า (orthostatic hypotension) 33 คน (ร้อยละ 40.2) ร้อยละ 70 ของผู้ป่วยที่มีภาวะดังกล่าวไม่มีอาการใดๆ จากการวิเคราะห์แบบ univariate และ multivariate ปัจจัยเสี่ยงของภาวะนี้คือ ระยะเวลาที่เป็นโรคพาร์คินสันมานาน ระยะท้ายๆของโรค และการได้รับยา selegiline*

สรุป: *ความถี่ของภาวะความดันต่ำหลังการเปลี่ยนท่า (orthostatic hypotension) ในผู้ป่วยโรคพาร์คินสันคือร้อยละ 40.2 ปัจจัยเสี่ยงของภาวะนี้คือระยะเวลาของการเป็นโรค ระยะท้ายๆ ของโรคพาร์คินสัน และการได้รับยา selegiline*