Sympathetic Hyperactivation as an Alternative Treatment of Orthostatic Hypotension in Parkinson's Disease: an Initial Report of an Ongoing Randomized Control Study

Thanawat Chungtanawiwat,
Parnsiri Chairangsaris

ABSTRACT

Background: Orthostatic hypotension (OH) is a common non-motor condition in Parkinson's disease (PD). For these individuals, pyridostigmine and midodrine have not been well compared.

Objective: To determine the safety and short-term effectiveness of pyridostigmine monotherapy in comparison to midodrine for individuals with Parkinson's disease who met the criteria for orthostatic hypotension (OH).

Materials and Methods: An open label, randomized clinical study was conducted. A total of thirteen PD patients with OH were enrolled and randomized to receive midodrine (5 mg/day) or pyridostigmine (120 mg/day) over a two-week period. The primary objective measured the degree of improvement in OH in two weeks. The secondary outcomes include changes in supine blood pressure (BP), supine heart rate (HR), and the proportion of patients who meet the BP criteria for OH. Note that this report was an interim analysis.

Results: The orthostatic BP of both groups was improved over two weeks. In comparison between groups, systolic blood pressure changes during supine to upright position were -14.6 mmHg and -15.4 mmHg for pyridostigmine and midodrine group, the orthostatic systolic BP (SBP) drop was significantly lower in the pyridostigmine group ($p = 0.029$ for pyridostigmine group and $p = 0.048$ for midrodrine group). The changes in orthostatic HR, supine SBP, supine DBP, and supine HR did not significantly differ between the two groups. Mild to moderate side effects were observed by five participants. While 42.9% of patients using midodrine met the BP criteria for OH, 33.3% of patients taking pyridostigmine did.

Thanawat Chungtanawiwat, MD.,Parnsiri Chairangsaris
3rd year Neurology Resident, Phramongkutklao Hospital
Neurology division, Department of Medicine, Phramongkutklao Hospital

Corresponding author:
Thanawat Chungtanawiwat, MD
3rd year Neurology Resident, Phramongkutklao Hospital, Bangkok, 10400 Thailand
E-mail : thanawat.duke@gmail.com

รับต้นฉบับ 31 มกราคม 2567, ปรับปรุงต้นฉบับ 2 พฤษภาคม 2567, ตอบรับต้นฉบับตีพิมพ์ 7 กรกฎาคม 2567

Conclusion: When treating orthostatic hypotension in Parkinson's disease patients, a single Pyridostigmine treatment was found to be safe and to be non-inferior to low dose Midodrine. Furthermore, it was discovered that pyridostigmine was better than midodrine in terms of enhancing orthostatic SBP change and reducing the number of OH patients.

Keywords: Pyridostigmine, Midodrine, Orthostatic hypotension, Parkinson's disease

Introduction

Blood pressure (BP) that drops further following a shift in upright position is known as orthostatic hypotension (OH). This condition is generally common in elderly people.[1] The sympathetic nervous system of the heart and the baroreflex are frequently affected in patients with Parkinson's disease (PD), which can result in OH. In addition to fatigue and shoulder or neck pain, the patient may develop syncope, unexplained falls, lightheadedness, cognitive impairment, impaired vision, and weakness. Orthostatic hypotension was detected in 40.2% of Parkinson's disease cases, according to a 10-month survey done at Phramongkutklao Hospital by Sithinamsuwan P, et al. In this group, the use of selegiline, a more advanced stage of Parkinson's disease, and a longer disease duration were risk factors for developing OH.[2]

Midodrine was the first medication licensed by the US Food and Drug Administration that was shown to relieve OH and clinical symptoms in double-blind, placebo-controlled trials.[3,4] The active metabolite of midodrine, desglymidodrine, hydrolyzes to decrease orthostatic blood pressure drops, raise peripheral vascular resistance, and diminish venous pooling in the legs and splanchnic circulation. It does this by directly activating the alph-1-adrenoreceptors.[3]

Pyridostigmine is an acetylcholinesterase inhibitor that raises cholinergic signals and promotes sympathetic ganglionic neurotransmission. Pyridostigmine may only increase adrenergic tone when the patient is upright since autonomic ganglionic traffic is primarily initiated by orthostatic pressure and is negligible when the patient is supine. According to a few brief investigations, pyridostigmine induced a reduction in diastolic blood pressure (DBP) while standing without exacerbating supine blood pressure.[5,6]

Midodrine and pyridostigmine have been shown in some randomized clinical trials to be both safe and effective in treating OH.[3-5] The majority of these studies were conducted for shorter than 24 hours, and the patients included in them had OH brought on by a variety of neurological conditions, which limited their applicability. Although previous studies have shown that over 65 percent of PD patients experience OH within seven years of diagnosis,[7] there were very few PD patients involved in the trials. This suggests that little attention has been paid to OH treatment in PD patients. Pyridostigmine and midodrine have not been extensively researched for the treatment of OH in Parkinson's disease patients. In Thailand, by Limwatthana C, et al., a small, open label, randomized clinical investigation, thirteen patients with OH who had Parkinson's disease (PD) were randomly assigned to take either pyridostigmine 30 mg twice day (60 mg/day) or midodrine 2.5 mg twice day (5 mg/day) for a month. Pyridostigmine and midodrine were found to be safe in patients with Parkinson's disease who had OH, and following treatment, OH diminished. Pyridostigmine was found to be superior

to midodrine in terms of improving orthostatic SBP change and lowering the proportion of patients who met the BP threshold for OH (-6.43 mmHg, -19 mmHg, respectively, p = 0.022).[8]

In the present study, we conducted a randomized open-label parallel clinical trial to assess the safety and short-term effectiveness of pyridostigmine 60 mg twice a day (with two-time higher dosage than the study of Limwatthana C, et al.[8] compared to midodrine (5 mg/day) in treating OH in patients with Parkinson's disease.

Objectives

To assess the safety and short-term (two weeks) effectiveness of pyridostigmine and midodrine as a therapy for Parkinson PD patients who met the diagnostic criteria for orthostatic hypotension (OH).

Materials and Methods Study design

This report was an interim analysis of an ongoing randomized, open-label clinical trial that was conducted at the Neurology Division of Phramongkutklao Hospital from January 2024 onwards. This project protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Department (I0026/67).

Trial Population

The following patients met the inclusion criteria: 1) participants aged eighteen years old or older, 2) diagnosed with Parkinson's disease (PD) based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria, and 3) experiencing symptoms of orthostatic intolerance, such as headaches, dizziness, and fainting, when they visited the Neurology Division of Phramongkutklao Hospital. For patients to be eligible for OH, they had to have a drop in systolic blood pressure (SBP) of at least 20 mmHg or a decline in diastolic blood pressure (DBP) of at least 10 mmHg within three minutes of moving from a lying to a standing posture [9]. If the candidates were bedbound or unable to measure their blood pressure, those patients were excluded from the study.

Procedure

We collected medical histories and conducted physical examinations at baseline. Using a CARESCAPE TMV100 blood pressure monitor, orthostatic blood pressure (BP) and heart rate (HR) were recorded following 10 minutes of resting in the supine position and 3 minutes of moving from lying to the standing position.

Patients who were eligible were randomized to receive midodrine 2.5 mg twice daily (after breakfast and dinner) or pyridostigmine 60 mg twice daily (after breakfast and dinner) for a duration of two weeks in a 1:1 ratio by block of four, if they fulfilled the requirements for the OH diagnosis [9] and signed a consent form. The patients' PD medication regimens and dosages would not alter throughout the research. Orthostatic blood pressure and heart rate were rechecked two weeks after treatment. Monitoring and recording were taken on the patient's drug compliance, potential side effects, and concurrent medications.

Outcomes

Primary outcome was an improvement of orthostatic blood pressure within the following two weeks of treatment. The secondary outcomes

included the percentage of patients satisfying BP criteria for OH at 2 weeks, the change in supine blood pressure, and the change in orthostatic heart rate. What happened in terms of safety was an adverse outcome.

Statistical methods:

The primary and key secondary efficacy analyses included all PD patients who assigned randomization (intention-to-treat group) was done using the STATA/MP 12 in the model. All statistical data were shown as mean and standard deviation. The independent t-test, paired t-test, and Mann-Whitney test were used to measure the differences across groups. The Chi-square test, Fisher's exact test, and McNemar test were used to conduct discrete statistic data by percentage.

Results

Thirteen individuals (20.3%) out of the 64 individuals with Parkinson's were prior routinely identified for OH met the OH criteria at our Phramongkutklao Neurology clinic and Parkinson clinic cohort. Then, all the 13 patients were invited to participate in our study during January 2024. They were randomly allocated and enrolled (Figure 1). The patients on pyridostigmine and midodrine had mean ages of 71.5 and 69 years, respectively, with 66.7 and 57.1 percent of them being female. In terms of age and gender, the patients were well matched. The duration of PD lasted three years in the pyridostigmine group and eight years in the midodrine group. In comparison to the pyridostigmine group, the midodrine group showed greater supine SBP at baseline (p = 0.0035). From the supine to the upright position, all patients showed a significant drop in their DBP (-1.1, - 4.9 mmHg) and SBP (-14.5, -15.1 mmHg). At baseline, orthostatic blood pressure and heart rate fluctuations were similar throughout the groups. Demographic characteristics were shown in Table 1.

for the primary outcome, the orthostatic blood pressure declines in both groups, however, they were better at two weeks after the treatment. In comparison between groups, the pyridostigmine group experienced a considerably more orthostatic SBP change (-14.5 mmHg and -15.4 mmHg for pyridostigmine and midodrine groups. The decrease in orthostatic DBP drop was not significantly different between the two groups (-1.17 mmHg and -4.86 mmHg for pyridostigmine and midodrine respectively, p = 0.142).

for secondary outcomes. Two weeks following therapy, there was no discernible difference between the two groups' orthostatic HR change, supine SBP, supine DBP, or supine HR change from baseline. There was a substantially decrease supine SBP in the pyridostigmine group (-11.3 mmHg, p = 0.0035), Table 2. It was found that 33.3 percent of the pyridostigmine patients and 42.9 percent of the midrodrine patients met the BP requirement for OH after two weeks of treatment. None of the patients exhibited any signs of OH (Table 3).

Adverse events

Out of 13 patients, 5 (38.5%) experienced adverse events. All adverse events were mild and transient which disappeared within a few days. Four patients (57.1%) in the pyridostigmine group developed dizziness (n = 2) and gastrointestinal symptoms, including nausea and diarrhea (n = 2), while one patient (16.7%) in the midodrine group reported nauseated.

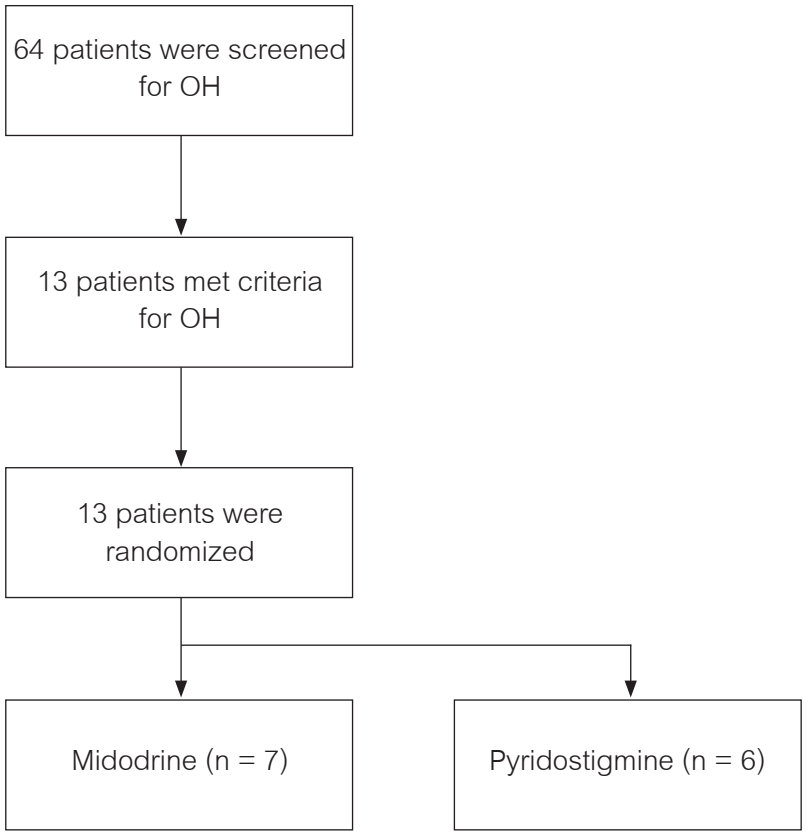

Figure 1. Flow diagram of the study

Table 1 Demographics of patients

	Pyridostigmine (n=6)	Midodrine (n=7)	p-value
Gender			
male	2 (33.33%)	3 (42.86%)	0.999
female	4 (66.67%)	4 (57.14%)	
Age			
Mean ± SD	71.50 ± 10.25	69.00 ± 13.54	0.719
median (Min - Max)	74 (58 - 85)	67 (54 - 88)	
Body weight (kg)			
Mean ± SD	55.5 ± 10.80	49.29 ± 5.44	0.206
median (Min - Max)	52 (44 - 69)	50 (42 - 58)	
Height (cm)			
Mean ± SD	158.67 ± 8.96	155.57 ± 8.06	0.525
median (Min - Max)	156.5 (149 - 170)	151 (149 - 171)	
BMI (kg/m2)			
Mean ± SD	22.11 ± 4.30	20.34 ± 1.39	0.372
median (Min - Max)	21.99 (16.61 - 28.3)	20.03 (18.86 - 22.22)	

	Pyridostigmine (n=6)	Midodrine (n=7)	p-value
Hypertension	3 (50.00%)	3 (42.86%)	0.999
Diabetic mellitus	2 (33.33%)	3 (42.86%)	0.999
Cardiovascular	1 (16.67%)	0 (0%)	0.462
Duration of Parkinson's disease (yr)			
Mean ± SD	2.67 ± 1.37	8.86 ± 6.12	
median (Min - Max)	2.5 (1 - 5)	8 (3 - 20)	0.014

Chi-square test or Fisher's exact test

Independent t-test or Mann-Whitney U test

significant iff p<0.05

Table 2 Baseline and follow-up orthostatic blood pressure and heart rate

	Pyridostigmine (n=6) Mean ± SD	Modrine (n=7) Mean ± SD	p-value**
Supine SBP, mmHg			
Baseline	140.17 ± 18.08	138.14 ± 16.1	0.835
2 weeks	128.83 ± 14.52	135.14 ± 13.57	0.435
p-value*	0.035	0.624	
Mean change (95% CI)	-11.33 (-21.46 , -1.21)	-3 (-17.23 , 11.23)	0.277
Orthostatic SBP drop, mmHg			
Baseline	-33.5 ± 15.37	-30.29 ± 12.58	0.686
2 weeks	-14.5 ± 7.34	-15.43 ± 10.37	0.858
p-value*	0.029	0.048	
Mean change (95% CI)	19 (2.95 , 35.05)	14.86 (0.16 , 29.55)	0.643
Supine DBP, mmHg			
Baseline	69.67 ± 13.28	74.57 ± 8.38	0.435
2 weeks	71 ± 11.66	76.14 ± 7.54	0.358
p-value*	0.563	0.376	
Mean change (95% CI)	1.33 (-4.21 , 6.87)	1.57 (-2.46 , 5.6)	0.931
Orthostatic DBP drop, mmHg			
Baseline	-1.17 ± 4.45	-6.29 ± 8.1	0.196
2 weeks	-1.17 ± 3.6	-4.86 ± 4.63	0.142
p-value*	0.999	0.578	
Mean change (95% CI)	0 (-4.3 , 4.3)	1.43 (-4.51 , 7.37)	0.649
supine HR, bpm			
Baseline	77.5 ± 21.49	81 ± 15.32	0.739
2 weeks	79.17 ± 19.54	81.86 ± 13.51	0.775
p-value*	0.153	0.744	
Mean change (95% CI)	1.67 (-0.88 , 4.21)	0.86 (-5.29 , 7)	0.784

* Paired t-test

** Independent t-test significant iff p<0.05

Table 3 Baseline and follow-up orthostatic hypotension

	Pyridostigmine (n=6)	Midodrine (n=7)	p-value
Patients met OH (n)			
Baseline	6 (100.00%)	7 (100.00%)	N/A
2 weeks	2 (33.33%)	3 (42.86%)	0.999
p-value	0.046	0.046	
Symptomatic OH (n)			
Baseline	1 (16.67%)	3 (42.86%)	0.559
2 weeks	0 (0%)	0 (0%)	N/A

Fisher's exact test

significant iff $p<0.05$

Discussion

The autonomic nerve system fails to regulate blood pressure in response to changes in posture because of insufficient norepinephrine release, which causes OH and supine hypertension, which is common in Parkinson's disease. However, there is still a deficiency in the treatment of symptomatic neurogenic orthostatic hypotension (nOH), which is sometimes complicated by significant rises in supine blood pressure. An effective treatment option for symptomatic nOH in Parkinson's disease (PD) is droxidopa, an oral prodrug that decarboxylates to norepinephrine. It improves nOH symptoms, falls, daily activities, and standing blood pressure.[10] Conversely, droxidopa is rather expensive and only available in a few nations. For PD patients, other drugs like midodrine or pyridostigmine may be a good substitute because they are more widely available and less expensive.

In this study, two weeks after therapy, orthostatic blood pressure changes and related symptoms were significantly alleviated by pyridostigmine and midodrine. After two weeks of medication, only 33.3% of the pyridostigmine group and 42.9% of the midodrine group experienced orthostatic hypotension. Overall, midodrine performed better at OH in DBP changes than pyridostigmine did, although pyridostigmine was better at OH in BP changes and reducing OH-associated symptoms, nevertheless, there were no statistic significant differences between studied groups.

Ours was one of the few studies to assess the safety and short-term effectiveness of pyridostigmine and midodrine for up to two weeks. In both groups, the SBP and DBP declines following standing were significantly reduced after two weeks. Pyridostigmine treatment decreased orthostatic blood pressure decline, although only slightly, up to six hours after delivery, according to short-term research.[5] Our research, pyridostigmine by far, it was recognized that both medications may be beneficial within a two-week period. Compared to another research from our division conducted earlier[8], Limwatthana C, et al. used a lower dosage of pyridostigmine (60 mg/day) for longer duration of follow up (4-week), which the results seemed not different.

When treating OH, supine hypertension is frequently a problem. Previous studies have demonstrated that pyridostigmine can lower the risk of supine hypertension.[5,6] In this study, there was a significant difference in the supine DBP change in

the midodrine group but not in the supine SBP change between the two groups. Long-term pyridostigmine treatment may raise supine SBP because it leads to occasional sympathetic hyperactivation[6]. Furthermore, the absence of supine hypertension in the midodrine group may be explained by the modest dose of midodrine used in this investigation.

Among the study's limitations were its small sample size (n = 13, as this report was the first initial assessment part from our ongoing trial), its short duration of Parkinson's disease, and its lack of a severity staging for PD patients, which we planned to further complete those measures in the next analysis. Therefore, not all PD patients may benefit from this study's results. The concomitant medication usage and dosage of the patients, which may have affected their blood pressure were not recorded in this initial part of the study.

Nevertheless, the therapies alleviated orthostatic blood pressure parameters change and symptoms related to OH for up to two weeks, even at low doses of midodrine. It's uncertain how long treatment will need to continue for combating OH. According to this study, midodrine or pyridostigmine therapy should be administered for a minimum of two weeks. It is necessary to complete our ongoing RCT to identify the effectiveness of treatment in individuals with various OH etiologies and to ascertain the optimum amount of time for pharmacologic treatment of OH.

Conclusion

Regarding the management of orthostatic hypotension in Parkinson's disease, pyridostigmine treatment has been shown to be safe and non-inferior to low dose Midodrine. Pyridostigmine was also found to be more effective than midodrine at improving orthostatic SBP change and reducing the number of patients with hypotension.

Acknowledgements

We extend our gratitude to the consultants, physicians, participants, and caretakers in the Neurology Division of Phramongkutklao Hospital.

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