Efficacy of single or combined midodrine and pyridostigmine in orthostatic hypotension

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ABSTRACT

Objective: To evaluate the long-term (for up to 3 months) efficacy and safety of single or combined therapy with midodrine and pyridostigmine for neurogenic orthostatic hypotension (OH).

Methods: This was a randomized, open-label clinical trial. In total, 87 patients with symptomatic neurogenic OH were enrolled and randomized to receive 1 of 3 treatments: midodrine only, pyridostigmine only, or midodrine + pyridostigmine. The patients were followed up at 1 and 3 months after treatment. The primary outcome measures were improvement in orthostatic blood pressure (BP) drop at 3 months. Secondary endpoints were improvement of the orthostatic BP drop at 1 month and amelioration of the questionnaire score evaluating OH-associated symptoms.

Results: Orthostatic systolic and diastolic BP drops improved significantly at 3 months after treatment in all treatment groups. Orthostatic symptoms were significantly ameliorated during the 3-month treatment, and the symptom severity was as follows: midodrine only < midodrine + pyridostigmine < pyridostigmine only group. Mild to moderate adverse events were reported by 11.5% of the patients.

Conclusions: Single or combination treatment with midodrine and pyridostigmine was effective and safe in patients with OH for up to 3 months. Midodrine was better than pyridostigmine at improving OH-related symptoms.

Clinicaltrials.gov identifier: NCT02308124.

Classification of evidence: This study provides Class IV evidence that for patients with neurogenic OH, long-term treatment with midodrine alone, pyridostigmine alone, or both midodrine and pyridostigmine is safe and has similar effects in improving orthostatic BP drop up to 3 months.
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GLOSSARY

ANOVA = analysis of variance; **BDI** = Beck Depression Inventory; **BP** = blood pressure; **DBP** = diastolic blood pressure; **HR** = heart rate; **HRQOL** = health-related quality of life; **OH** = orthostatic hypotension; **OHDAS** = Orthostatic Hypotension Daily Activity Scale; **OHQ** = Orthostatic Hypotension Questionnaire; **SBP** = systolic blood pressure; **SF-36v2** = Short Form (36) Health Survey version 2.

Pharmacologic treatment is essential in managing orthostatic hypotension (OH).[1] Midodrine is the first US Food and Drug Administration–approved drug that has been shown to improve OH and clinical symptoms in double-blinded placebo-controlled trials.[2,3] This compound is hydrolyzed to its active metabolite, desglymidodrine, which directly activates the α^1-adrenoreceptors, which increase the peripheral vascular resistance, reduce venous pooling in the legs and splanchnic circulation, and improve orthostatic blood pressure (BP) drops.[4,5] Midodrine is effective for orthostatic BP control but worsens supine hypertension in a dose-dependent manner.[2]

Pyridostigmine is an acetylcholinesterase inhibitor that increases cholinergic signals and facilitates sympathetic ganglionic neurotransmission. Because autonomic ganglionic traffic

Supplemental data at Neurology.org

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is minimal in the supine position and is activated with orthostatic pressure, pyridostigmine may increase adrenergic tone only in the upright posture.[6] A few short-term studies have reported that pyridostigmine improved diastolic BP (DBP) drops during standing without aggravation of the supine BP but only slightly.[7,8]

Several randomized clinical trials have evaluated the short-term efficacy and tolerability of midodrine and pyridostigmine in patients with OH,[1,7,9] but the long-term benefits of these pharmacologic interventions remain unclear. Moreover, most such trials failed to evaluate the effect of these drugs on OH-associated symptoms and health-related quality of life (HRQOL). In addition, head-to-head comparisons of the 2 drugs and the probable benefit of combination treatment have not been properly evaluated.

In this study, we performed a randomized open-label parallel clinical trial to evaluate the long-term (3-month) efficacy and safety of midodrine and pyridostigmine in patients with OH.

METHODS

Study participants. Patients ≥18 years of age who visited the Neurology Department of Seoul National University Hospital and complained of symptoms of orthostatic intolerance (e.g., dizziness, lightheadedness, and feeling faint) were considered for inclusion. The inclusion criterion was symptomatic neurogenic OH determined by medical history and clinical examination. OH was defined as a systolic BP (SBP) reduction of ≥20 mm Hg or a DBP reduction of ≥10 mm Hg within 3 minutes of standing.[10] The exclusion criteria were OH caused by medication such as diuretics or β-blockers and significant systemic illness.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Institutional Review Board of the Seoul National University Hospital (1409-066-609) and was registered at ClinicalTrials.gov (NCT02308124). Written informed consent to participate was obtained from all enrolled patients.

Study design and procedures. This was a randomized, open-label parallel study. The primary endpoint was improvement of the orthostatic BP drop at 3 months after treatment. Secondary endpoints were improvement of the orthostatic BP drop at 1 month and amelioration of the questionnaire score evaluating OH-associated symptoms, depression, and QOL.

At baseline, we obtained medical histories, performed physical examinations, and administered self-reported questionnaires. Orthostatic BP and heart rate (HR) were measured after 10 minutes of rest in the supine position with a Welch Allyn BP monitor (Welch Allyn Protocol Inc, Beaverton, OR) and at 1, 3, 5, and 10 minutes after standing. Maximum decrements in SBP and DBP within 3 minutes of standing were recorded. Patients who met the inclusion criteria were than randomized to receive 1 of 3 treatments: midodrine only, i.e., 2.5 mg midodrine twice a day; pyridostigmine only, i.e., 30 mg pyridostigmine twice a day; and midodrine + pyridostigmine, i.e., a combination of 2.5 mg midodrine and 30 mg pyridostigmine twice a day. Randomization was done at the Seoul National University Hospital Clinical Research Unit with a list of computer-generated random numbers (block of size 3). The dose could be increased to 5 mg midodrine or 60 mg pyridostigmine twice a day at the clinician's discretion during follow-up. Low dose of midodrine and pyridostigmine was used to minimize adverse effect and possible dropouts. The patients were followed up at 1 and 3 months after treatment. Orthostatic BP and HR measurements and questionnaires were repeated. Drug compliance, possible side effects, and concomitant medications were checked at each visit. Medications affecting the autonomic nervous system and BP were discouraged during the trial.

Questionnaires. Three sets of self-reported questionnaires were administered before and at 1 and 3 months after the treatment. To evaluate OH-associated symptoms and disability, the OH Questionnaire (OHQ) was used. This questionnaire has 2 components: the OH Daily Activity Scale (OHDAS), which contains 4 items measuring the influence of OH on daily activities, and the OH Symptom Assessment, which contains 6 items measuring the symptoms of OH (dizziness/light headedness, vision disturbance, weakness, fatigue, trouble concentrating, and head/neck discomfort).[11] This questionnaire reflects the severity of OH-related symptoms on a 10-point scale, with 0 indicating the absence of a symptom and 10 indicating maximal severity. Depression was evaluated with the Beck Depression Inventory (BDI)-II, which comprises 21 multiple-choice questions, each of which can be scored from 0 to 3.[12] To assess HRQOL, Short Form (36) Health Survey version 2 (SF-36v2) was administered.[13] SF-36v2 measures 8 HRQOL domains (physical functioning, role limitation caused by physical problems, bodily pain, general health, vitality, social functioning, role limitation caused by emotional problems, and mental health) summarized into 2 summary scales that are normalized to the population (mean = 50, SD = 10): the physical component summary scale and the mental component summary scale.[14] Better HRQOL is reflected by higher SF-36v2 scores.

Classification of evidence. Primary research question was as follows: Can single or combined midodrine and pyridostigmine have different long-term effect in improving orthostatic BP drop in patients with neurogenic OH? This study provides Class IV evidence that for patients with neurogenic OH, long-term treatment with midodrine alone, pyridostigmine alone, or both midodrine and pyridostigmine is safe and has similar effects in improving orthostatic BP drop up to 3 months.

Outcomes. The primary endpoint was improvement of the orthostatic BP drop at 3 months after treatment. Maximum decrements in SBP and DBP within 3 minutes of standing were analyzed. Secondary endpoints were percentage of patients fulfilling BP criteria for OH at 1 and 3 months, improvement of the orthostatic BP drop at 1 month, and amelioration of the questionnaire score evaluating OH-associated symptoms, depression, and QOL at 1 and 3 months.

Safety endpoints were adverse events. The adverse events were defined as any unintended response thought to be related to treatment. Expected adverse reactions were listed in the protocol, and causality was determined by the treating physician. Common Terminology Criteria for Adverse Events (version 4.0)[15] was used to grade events, and severe adverse events were defined as grade 3 or more.

Table 1 Patient characteristics

	Total (n = 87)	Midodrine only (n = 29)	Pyridostigmine only (n = 29)	Midodrine + pyridostigmine (n = 29)	p Value
Age, y	57.2 ± 16.0	59.2 ± 17.7	59.7 ± 13.4	52.7 ± 16.2	0.179
Male, n (%)	41 (47.1)	15 (51.7)	12 (41.4)	14 (48.3)	0.724
Height, cm	161.7 ± 13.7	163.1 ± 10.3	151.8 ± 8.3	160.3 ± 19.9	0.740
Weight, kg	63.0 ± 11.0	62.3 ± 11.0	63.5 ± 10.6	62.3 ± 11.6	0.911
BMI, kg/m^2	25.0 ± 11.9	23.8 ± 3.2	24.2 ± 3.0	27.0 ± 20.2	0.536
Etiology, n (%)					0.286
Idiopathic OH	41 (47.1)	12 (41.4)	13 (44.8)	16 (55.2)	
MSA	4 (4.6)	1 (3.4)	3 (10.3)	0	
Diabetic PAN	20 (23.0)	9 (31.0)	8 (27.6)	3 (10.3)	
Nondiabetic PAN	22 (25.3)	7 (24.1)	5 (17.2)	10 (34.5)	

Abbreviations: BMI = body mass index; MSA = multiple system atrophy; OH = orthostatic hypotension; PAN = peripheral autonomic neuropathy.
Data are presented as mean ± SD when appropriate.

Statistical analysis. All data are presented as mean ± SD. All analyses were done on the intention-to-treat principle, and missing values were excluded from the analysis. Initially, we compared group differences in supine and orthostatic BP, HR, and questionnaire scores at each time point. Continuous data were compared by 1-way analysis of variance (ANOVA), and the χ^2 test was used to analyze categorical data. Then, we evaluated changes from baseline to 1 or 3 months after treatment by performing a paired t test for each group. Repeated-measures ANOVA with the treatment group as the between-subject factor and time (baseline and 1 and 3 months after treatment) as the within-subject factor was used to test for an overall difference in treatment effects. Post hoc analysis was performed with the Tukey test. The Pearson correlation coefficient was determined to assess the relationship between changes in orthostatic BP drops and OH-associated symptoms or HRQOL at 3 months after treatment. Data were analyzed with SPSS 22.0 for Windows, and the significance was set at $p < 0.05$.

RESULTS

Clinical features and baseline characteristics. A total of 87 patients were finally enrolled and randomized (figure e-1 at Neurology.org). The mean age was 57.2 years, and 41 (47.1%) were male. The patients were well matched by age and sex. Twenty-two patients had nondiabetic peripheral autonomic neuropathy; 20 patients had diabetic autonomic neuropathy; 4 patients had multiple system atrophy; and 41 patients had unspecified OH (table 1).

At baseline, the midodrine-only group had higher supine SBP than the pyridostigmine-only (post hoc $p = 0.025$) and midodrine + pyridostigmine (post hoc $p = 0.006$) groups. All patients exhibited substantial decreases in SBP (−23.5 ± 10.8 mm Hg) and DBP (−14.1 ± 9.0 mm Hg) from the supine to the upright position without profound increases in HR (12.9 ± 9.9 bpm). Orthostatic BP, HR changes, and questionnaire scores, including OHQ, BDI, and SF-36v2, were comparable between the groups at baseline.

Number of patients who met BP criteria for OH at the 1- and 3-month follow-ups. At 1 month after treatment, 78 patients were evaluated, and 47.4% of them met the BP criteria for OH. Sixty-five patients were evaluated at 3 months, and 43.1% met the criteria. The proportion of the patients who met BP criteria for OH did not differ among treatment groups at 1 and 3 months ($p = 0.841$, $p = 0.459$, respectively). The proportion of patients who met the BP criteria was the lowest at 3 months in the midodrine + pyridostigmine group (33.3%), which was much lower than that at 1 month (51.9%). However, the proportions were similar in the midodrine-only and pyridostigmine-only groups at 3 months compared with those at 1 month (table 2).

Twenty-two patients were lost to follow-up at 3 months, and demographics, initial supine or orthostatic vital signs, and treatment modalities were similar between those who completed the study and those who did not (table e-1). The results of SF-36v2 were not obtained in 4 patients (1 in the midodrine-only group and 3 in the pyridostigmine-only group), and the BDI was not obtained in 1 patient in the midodrine-only group.

Orthostatic vital signs at the 1- and 3-month follow-ups. The orthostatic BP drop improved in all treatment groups at 1 and 3 months without HR changes. At 1 month after treatment, both orthostatic SBP and DBP drops were reduced in the midodrine + pyridostigmine group ($p = 0.007$, $p = 0.001$, respectively). In contrast, the midodrine-only group showed improvement in orthostatic SBP only, and the pyridostigmine-only group showed improvement in orthostatic DBP drops only. At 3 months, the orthostatic SBP and DBP drops had decreased in all treatment groups. No significant difference in the

Table 2 Orthostatic vital signs at baseline and 1 and 3 months

	Total	Midodrine	Pyridostigmine	Midodrine + pyridostigmine	*p* Value[a]
Patients who meet BP criteria for OH, n (%)					
Baseline	87	29	29	29	
1 mo	37/78 (47.4)	11/25 (44.0)	12/26 (46.2)	14/27 (51.9)	0.841
3 mo	28/65 (43.1)	10/23 (43.5)	11/21 (52.4)	7/21 (33.3)	0.459
Orthostatic SBP drop, mm Hg					
Baseline	−23.5 ± 10.8	−24.7 ± 9.9	−23.3 ± 12.5	−22.5 ± 10.1	0.732
1 mo	−14.3 ± 16.3[b]	−12.6 ± 16.4[b]	−17.4 ± 18.5	−12.9 ± 14.0[b]	0.498
3 mo	−11.9 ± 13.0[b]	−12.2 ± 12.8[b]	−11.7 ± 14.7[b]	−11.9 ± 12.0[b]	0.990
Orthostatic DBP drop, mm Hg					
Baseline	−14.1 ± 9.0	−13.4 ± 9.0	−15.5 ± 9.9	−13.4 ± 8.2	0.59
1 mo	−4.1 ± 14.9[b]	−7.8 ± 16.4	−1.6 ± 14.0[b]	−3.1 ± 13.6[b]	0.303
3 mo	−5.2 ± 12.3[b]	−5.0 ± 12.6[c]	−4.2 ± 13.2[c]	−6.6 ± 11.5[c]	0.809
Orthostatic HR change, bpm					
Baseline	12.9 ± 9.9	11.9 ± 13.5	13.8 ± 9.1	13.0 ± 5.8	0.783
1 mo	13.3 ± 8.1	12.4 ± 7.5	13.6 ± 8.4	13.9 ± 8.7	0.783
3 mo	11.2 ± 7.5[d]	10.4 ± 4.8	10.7 ± 9.2	12.6 ± 8.1	0.591
Supine SBP, mm Hg					
Baseline	127.9 ± 19.4	137.3 ± 20.9	124.5 ± 18.5	122.0 ± 15.6	0.004
1 mo	134.2 ± 19.4[b]	136.9 ± 18.5	132.5 ± 21.5[c]	133.3 ± 18.4[b]	0.701
3 mo	132.8 ± 19.6[c]	131.4 ± 17.3	135.1 ± 22.5[c]	131.8 ± 19.3[b]	0.787
Supine DBP, mm Hg					
Baseline	78.9 ± 11.4	83.2 ± 12.8	76.5 ± 9.8	76.9 ± 10.4	0.041
1 mo	79.6 ± 15.0	82.7 ± 14.0	76.2 ± 14.7	80.0 ± 16.0	0.297
3 mo	77.9 ± 14.0	77.8 ± 12.4	74.1 ± 14.6	81.8 ± 15.0[c]	0.226
Supine HR, bpm					
Baseline	67.2 ± 11.8	68.0 ± 11.3	66.7 ± 13.5	67.0 ± 10.7	0.9
1 mo	69.5 ± 11.0[c]	69.6 ± 11.8	69.5 ± 12.9	69.3 ± 8.3	0.995
3 mo	69.5 ± 12.2	69.0 ± 13.2	70.8 ± 12.4	68.6 ± 11.2	0.818

Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; HR = heart rate; OH = orthostatic hypotension; SBP = systolic blood pressure.
Data are presented as mean ± SD when appropriate.
[a] *p* Value from 1-way analysis of variance or χ^2 test.
[b] $p < 0.01$ vs baseline by the paired *t* test.
[c] $p < 0.05$ vs baseline.
[d] $p < 0.05$ vs 1 month.

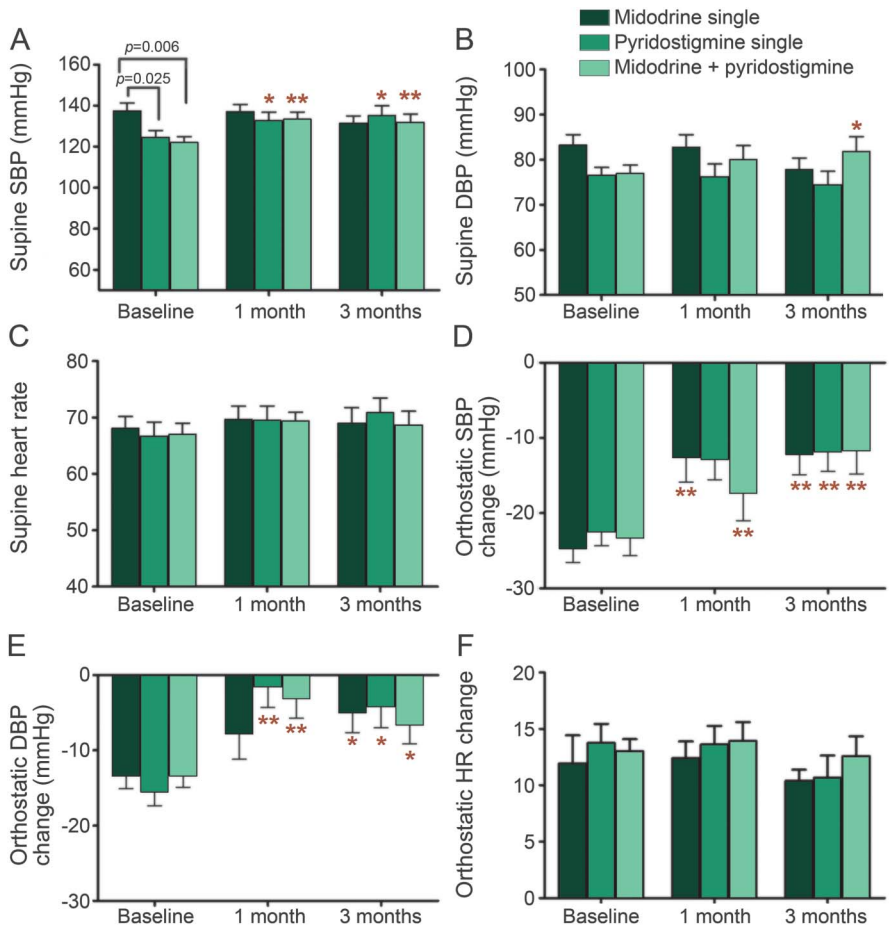
degree of orthostatic BP drop was observed between the groups at 1 and 3 months.

The supine SBP increased in the pyridostigmine-only and midodrine + pyridostigmine groups at 1 and 3 months after treatment but not in the midodrine-only group. The supine DBP only increased in the midodrine + pyridostigmine group at 3 months relative to the baseline value (figure 1 and table 2).

Repeated-measures ANOVA revealed time effects on orthostatic SBP drops, DBP drops, and supine SBP, but no significant effect of the treatment group was observed. Only the supine SBP showed a group-by-time interaction ($F_{4,126} = 3.308$, $p = 0.013$) (table e-2).

Questionnaire scores at 1- and 3-month follow-ups. The questionnaire scores and use of antidepressants are listed in table 3. The midodrine-only group showed lower total OHQ and BDI scores at 1 month and decreased OHDAS scores at 1 and 3 months compared to the pyridostigmine-only group. Relative to the baseline values, the orthostatic symptom and disability scores at 3 months were improved in all groups. In addition, the BDI and SF-36 mental component summary scale scores improved in the single-drug treatment groups at 3 months but not in the combination group. Compared with the scores at 1 month, the total OHQ, OH Symptom Assessment, and BDI scores decreased in the midodrine-only and

Figure 1 Supine and orthostatic vital signs at baseline and 1 and 3 months after administration of study drug



DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure. *$p < 0.05$ vs baseline, **$p < 0.01$ vs baseline by the paired t test.

pyridostigmine-only groups at 3 months but not in the combination group. The use of antidepressants was similar among the groups at all time points (figure 2 and table 3).

Repeated-measures ANOVA revealed significant time effects on all questionnaire scores. A group effect was seen in OHQ total ($F = 3.482$, $p = 0.037$) and OHDAS ($F = 3.930$, $p = 0.025$), with midodrine single < midodrine + pyridostigmine < pyridostigmine single. Only BDI score had a group-by-time interaction ($F_{4,124} = 2.480$, $p = 0.047$) (table e-2). Improvement in BDI score at 1 month was greater in the midodrine-only group than the midodrine + pyridostigmine group (BDI score change at 1 month: midodrine only -4.4 ± 3.6 vs midodrine + pyridostigmine -2.1 ± 4.5, $p = 0.047$).

Association between decreased orthostatic BP drop and improvement in symptoms. To evaluate whether the improvement in orthostatic BP was associated with amelioration of the associated symptoms, we evaluated the correlation between changes in orthostatic BP drop within 3 months of treatment and the degree of improvement in the questionnaire scores. Association was observed only between orthostatic DBP drop and SF-36 mental component summary scale improvement ($r = 0.299$, $p = 0.018$, figure e-2); no significant associations were found between changes in orthostatic BP drop and the OHQ and BDI scores.

Adverse events. Ten of 87 patients (11.5%) reported adverse events, and the proportion did not differ between treatment modalities ($p = 0.111$). All adverse events occurred within 1 month and were grade 1 or 2 (mild to moderate) in severity.[15] One patient (4.3%) in the midodrine-only group reported headache and aggravated dizziness. Six patients (25.0%) in the pyridostigmine-only group reported aggravated dizziness (n = 5); headache (n = 2); gastrointestinal symptoms, including nausea and diarrhea (n = 2); or limb tremors (n = 1). Three patients in the midodrine + pyridostigmine group (11.5%) reported abdominal pain and nausea (n = 2), dizziness (n = 1), or visual disturbances (n = 1). Four of 87 patients (4.6%) (2 patients in the pyridostigmine-only group and 2 patients in the

Table 3 Antidepressant use and questionnaire scores at baseline and 1 and 3 months

	Total	Midodrine	Pyridostigmine	Midodrine + pyridostigmine	*p* Value[a]
OHQ total score					
Baseline	33.4 ± 21.0	31.0 ± 22.5	37.2 ± 22.0	32.0 ± 18.6	0.488
1 mo	21.2 ± 18.3[b]	16.0 ± 17.8[b]	27.6 ± 21.4	20.0 ± 13.8[b]	0.048
3 mo	16.9 ± 15.4[b,c]	11.7 ± 10.1[b,c]	22.6 ± 20.6[b]	16.5 ± 12.0[b]	0.058
OHDAS					
Baseline	12.4 ± 10.4	11.6 ± 10.1	14.0 ± 10.9	11.7 ± 10.4	0.613
1 mo	8.6 ± 8.9[b]	6.2 ± 7.4[b]	12.1 ± 11.1	7.5 ± 6.9[b]	0.041
3 mo	5.7 ± 7.7[b,c]	2.7 ± 3.7[b,c]	8.6 ± 9.6[b]	5.9 ± 7.8[b]	0.035
OHSA					
Baseline	21.0 ± 12.2	19.5 ± 13.4	23.2 ± 12.9	20.3 ± 10.3	0.472
1 mo	15.0 ± 10.5[b]	12.4 ± 11.0[b]	18.7 ± 11.2[b]	13.9 ± 8.5[b]	0.081
3 mo	11.2 ± 8.7[b,c]	9.0 ± 7.0[b,d]	14.0 ± 11.6[b,d]	10.6 ± 5.7[b]	0.146
BDI					
Baseline	13.4 ± 7.8	13.6 ± 6.8	15.1 ± 8.6	11.7 ± 7.9	0.253
1 mo	10.3 ± 5.4[b]	8.9 ± 4.7[b]	12.4 ± 6.2[b]	9.5 ± 4.5[e]	0.04
3 mo	6.9 ± 4.3[b,c]	6.1 ± 4.3[b,c]	7.2 ± 4.7[b,c]	7.3 ± 3.9	0.6
SF-36v2, physical component					
Baseline	42.0 ± 8.6	40.9 ± 8.4	42.0 ± 9.3	43.2 ± 8.2	0.585
1 mo	44.7 ± 6.3[b]	44.9 ± 6.9[b]	42.6 ± 7.1	46.5 ± 4.0[b]	0.068
3 mo	46.6 ± 6.7[b,d]	48.3 ± 5.3[b,d]	44.2 ± 7.4	46.9 ± 6.9	0.143
SF-36v2, mental component					
Baseline	43.4 ± 9.0	43.4 ± 8.4	41.1 ± 9.4	45.7 ± 8.8	0.147
1 mo	44.1 ± 7.8	44.4 ± 8.6	42.7 ± 7.3	45.3 ± 7.4	0.458
3 mo	47.9 ± 6.7[b,c]	48.4 ± 7.2[e]	47.4 ± 7.9[b,c]	47.7 ± 5.0	0.892
Use of antidepressants, n (%)					
Baseline	21/87 (24.1)	9/29 (31.0)	5/29 (17.2)	7/29 (24.1)	0.471
1 mo	19/78 (24.4)	6/25 (24.0)	6/26 (23.1)	7/27 (25.9)	0.970
3 mo	15/65 (23.1)	5/23 (21.7)	5/21 (23.8)	5/21 (23.8)	0.987

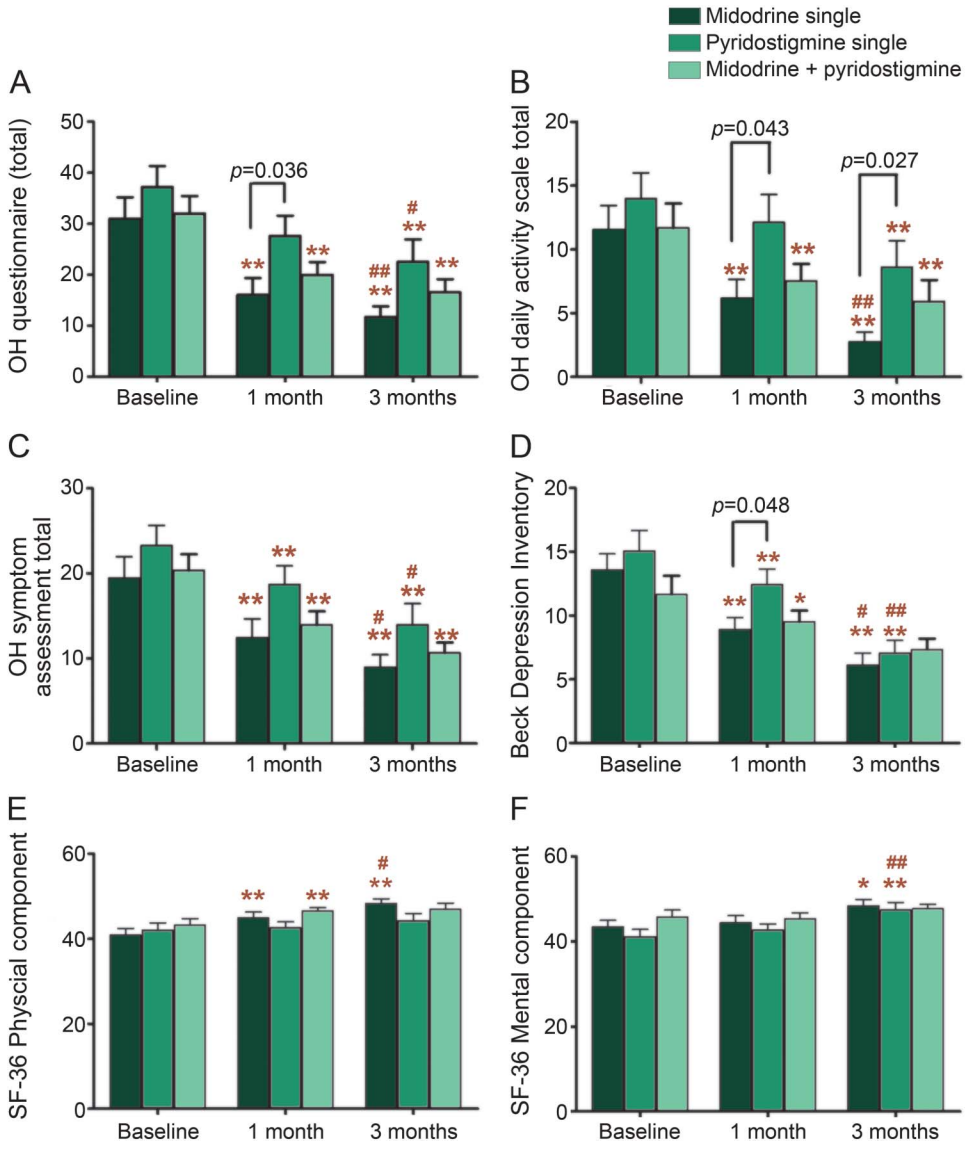
Abbreviations: BDI = Beck Depression Inventory; OH = orthostatic hypotension; OHDAS = Orthostatic Hypotension Daily Activity Scale; OHQ = Orthostatic Hypotension Questionnaire; OHSA = Orthostatic Hypotension Symptom Assessment; SF-36v2 = Short Form (36) Health Survey version 2.
Data are presented as the mean ± SD when appropriate.
[a] *p* Value from 1-way analysis of variance or χ^2 test.
[b] $p < 0.01$ vs baseline by paired *t* test.
[c] $p < 0.01$ vs 1 month by paired *t* test.
[d] $p < 0.05$ vs 1 month.
[e] $p < 0.05$ vs baseline.

midodrine + pyridostigmine group) discontinued or changed treatments because of the side effects (gastrointestinal symptoms or dizziness); the other adverse effects resolved spontaneously.

DISCUSSION Midodrine and pyridostigmine significantly improved orthostatic BP changes and associated symptoms at 3 months after treatment. Fewer than half of the patients met the BP criteria for OH at 1 month (47.4%) and 3 months (43.1%) after treatment. Overall, midodrine was better at ameliorating OH-associated symptoms than pyridostigmine. The combination of the 2 drugs demonstrated beneficial effects in controlling orthostatic BP drops but failed to show better improvement in OH-related symptoms. This study was the first to evaluate long-term efficacy and safety of midodrine or pyridostigmine up to 3 months.

The SBP and DBP drops after standing were significantly decreased after 3 months in the midodrine- and pyridostigmine-only and combination treatment groups. A short-term study revealed that pyridostigmine treatment improved orthostatic BP drop but only slightly up to 6 hours after administration.[7] Our study suggests that pyridostigmine alone can

Figure 2 Questionnaire scores at baseline and 1 and 3 months after administration of study drug



OH = orthostatic hypotension; SF-36 = Short Form (36) Health Survey. *$p < 0.05$ vs baseline, **$p < 0.01$ vs baseline by the paired *t* test, #$p < 0.05$ vs 1 month, ##$p < 0.01$ vs 1 month by the paired *t* test.

be effective for the long-term management of OH. Pyridostigmine had effects on standing BP drop similar to those of midodrine for up to 3 months.

The combination of midodrine and pyridostigmine most effectively controlled orthostatic BP changes. The combined group exhibited improvements in both SBP and DBPs drop at 1 month. In contrast, the midodrine-only group showed improvement in the SBP drop, and the pyridostigmine-only group showed improvement in the DBP drop. Short-term studies have reported that midodrine exerts more prominent effects on standing SBP[16] and that pyridostigmine affects standing DBP more strongly[7]; however, the mechanism underlying this difference remains unclear.

Orthostatic symptoms consistently improved 3 months after treatment. A previous meta-analysis reported that the odds ratio for orthostatic symptom improvement with midodrine was 3.9 compared with controls.[9] However, the longest follow-up period of the studies involved was only 6 weeks. Our results suggest that patients may obtain additional benefit from the long-term use of midodrine (i.e., >1 month). The effects of pyridostigmine on orthostatic symptoms have been evaluated by only a few short-term studies, and contradictory results have been reported.[6,8] One study evaluated symptom improvement at 1 hour after pyridostigmine treatment,[6] whereas another reported no significant improvement in presyncopal symptoms.[8] Our study revealed that pyridostigmine was less effective at controlling OH symptoms than midodrine. Because pyridostigmine can affect the CNS and cause depressed mood,

lethargy, and sleep disturbances,[17] it may be responsible for the decreases in the subjective symptom scores.

Pharmacologic treatment for OH also improved depression and HRQOL, which have not been properly evaluated in previous reports. Depressive symptoms and HRQOL improved in the single-treatment groups at 3 months, although, contrary to our expectation, the combination treatment group showed no significant improvement. The degree of improvement in the BDI-II score was less significant in the combination group than in the midodrine-only group. Indeed, taking multiple medications for a long time can be burdensome for patients. The adverse effects of pyridostigmine on mood may also have affected the results. Combining midodrine with a medication other than pyridostigmine, such as droxidopa, should be evaluated in future studies.

Supine hypertension is always a concern in OH treatment. Pyridostigmine is known to cause less supine hypertension, although in this study, the pyridostigmine-only group showed significant increases in supine SBP at 1 and 3 months. Because pyridostigmine can cause intermittent sympathetic hyperactivation,[6] its long-term use can increase supine SBP, as suggested in a previous case report.[18] However, because the midodrine-only group had higher values of baseline supine SBP than the other groups, we could not directly compare the risk of supine hypertension between treatment groups. In addition, the low dose of midodrine used in this study may be the reason why the supine hypertension was not worse in the midodrine-single group.

Although this study was performed in a single center without a placebo group and a blinding process, it must be acknowledged that this is the longest study ever performed with a randomized design to evaluate the long-term efficacy of midodrine and pyridostigmine. Initial doses of midodrine and pyridostigmine used for this study were lower than maximal doses used to treat OH; thus, the efficacy of treatment may have been underestimated. However, even with the low dose, the treatments improved hemodynamic parameters and symptoms associated with OH up to 3 months. Compared with previous studies,[3,8,16,18] which focused on primary autonomic degenerative disorders, the most identified etiology in our study was peripheral autonomic neuropathy, except for 4 patients with multiple system atrophy. Additional studies evaluating the treatment efficacy in patients with different OH etiologies may be warranted.

The short-term use of midodrine + pyridostigmine followed by the long-term use of midodrine alone may be an optimal strategy for managing OH. OH is thought to require long-term treatment; however, the actual duration of treatment required remains unclear. This study suggests that treatment with midodrine or pyridostigmine should be continued for at least 3 months. Further studies with longer follow-up are necessary to determine the optimal duration of pharmacologic treatment of OH.

AUTHOR CONTRIBUTIONS

Dr. J.I. Byun analyzed and interpreted the data, performed the statistical analysis, and wrote the manuscript. Dr. J. Moon analyzed and interpreted the data and wrote the manuscript. D.Y. Kim and Dr. H. Shin acquired and analyzed the data. Dr. J.S. Sunwoo, Dr. J.A. Lim, Dr. T.J. Kim, Dr. W.J. Lee, Dr. H.S. Lee, and Dr. J.S. Jun acquired, analyzed, and interpreted the data. Dr. K.I. Park, Dr. S.T. Lee, Dr. K.H. Jung, and Dr. K.Y. Jung made critical revision of the manuscript. Dr. Lee and Dr. K. Chu established the study idea and made critical revision of the manuscript.

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DISCLOSURE

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