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A Comparative Efficacy of Midodrine, Pyridostigmine and Atomoxetine in Neurogenic Orthostatic Hypotension

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Abstract

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Midodrine is the mainstay treatment, and pyridostigmine and atomoxetin are common drugs used for patients with orthostatic hypotension (OH). However, information regarding the long-term effectiveness and safety of these drugs in OH is lacking. Moreover, head-to-head comparisons and possible synergistic effects have not yet been investigated. In this study, we aimed to evaluate the long-term efficacy and safety of midodrine, pyridostigmine, and atomoxetin for OH.

We performed two prospective open-label randomized trial, and enrolled patients with symptomatic neurogenic OH. In the first trial, we randomly assigned in a 1:1:1 ratio to receive 1 of 3 treatments: (1) midodrine 5mg/day; (2) pyridostigmine 60mg/day; and (3) midodrine 5mg/day + pyridostigmine 60mg/day and followed-

up at 1 and 3 months after treatment. We also performed an adjunctive study to evaluate the efficacy of the midodrine or pyridostigmine for patients with delayed OH. In the second trial, we randomly assigned in a 1:1 ratio to receive (1) midodrine 5mg twice a day; (2) atomoxetine 18mg once a day and followed-up at 1 month after treatment. The primary outcome measures were improvement in orthostatic blood pressure (BP) drop at 1 and 3 months. Secondary end-points were amelioration of questionnaire score evaluating OH-associated symptoms. Safety endpoint was adverse events. Analysis was done by intention to treat.

In the First trial, 120 patients were screened and, of those, 87 were randomly assigned. Orthostatic systolic blood pressure (SBP) and diastolic blood pressure (DBP) drops improved significantly at 3 months after treatment in all treatment groups, and mean changes in the SBP and DBP drop were not significantly different. 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. Result of the adjunctive study showed that questionnaire scores were comparable between the classic and delayed OH, and OH-related symptoms significantly improved after 3 months of the treatment. In the second trial we screened 54 patients and randomly assigned 50 of them to receive either midodrine or atomoxetine. Orthostatic SBP and DBP drop improved significantly at 1 month after the treatment, which were similar between the two groups. Orthostatic symptoms improved only in patients who received

atomoxetine, and depression and quality of life improved in both groups. Mild to moderate adverse events were reported by 4.0% of the patients in the second trial. Midodrine, pyridostigmine, and atomoxetine were all effective and safe in patients with neurogenic OH. Midodrine was better than pyridostigmine, and atomoxetine was even better than the midodrine at improving OH-related symptoms. Combination treatment may be more effective for orthostatic BP control but not for OH-related symptoms.

Keyword: Orthostatic hypotension; Midodrine; Pyridostigmine; Atomoxetine; Efficacy

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List of Abbreviations

ANOVA: analysis of variance

BDI-II: Beck Depression Inventory-II

BMI: body-mass index

BP: blood pressure

CTCAE: Common Terminology Criteria for Adverse Events

DBP: diastolic blood pressure

FDA: Food and Drug Administration

HR: heart rate

HRQOL: health-related quality of life

MBP: mean blood pressure

MCS: mental component summary scale

NOH: neurogenic orthostatic hypotension

OH: orthostatic hypotension

OHDAS: Orthostatic hypotension daily activity scale

OHQ: Orthostatic hypotension questionnaire

OHSA: Orthostatic hypotension symptom assessment

PCS: physical component summary scale

SBP: systolic blood pressure

SF-36v2: Short Form (36) Health Survey version 2

I. Introduction

1. Orthostatic Hypotension

Classic definition of Orthostatic hypotension (OH) is a systolic blood pressure (SBP) drop of at least 20 mmHg or a diastolic blood pressure (DBP) drop of at least 10 mmHg within 3 minutes of standing or upright tilt table testing to 60 degrees(1). Prevalence of OH increases with age and comorbidities. It is reported to be 30% in adult age above 65 years(2) and increases up to 64% in inpatient settings(1). About 30% with type 1 or 2 diabetes patients have OH(3). OH can lead to lightheadedness, weakness, dizziness, and syncope(4, 5) It is also associated with an increased incidence of cerebrovascular disease, myocardial infarction, and mortality(6-8) and an increased risk of depression(9) and reduced health-related quality of life (HRQOL)(10).

OH can be clinically classified into several categories. Apart from classic OH, delayed OH is referred when the blood pressure (BP) drop occurs beyond 3 minutes. It is also recognized as a potential etiology of orthostatic intolerance(1, 11). Among 230 patients with orthostatic intolerance, less than half(46%) exhibited a BP drop within 3 minutes, 15% had a BP drop between 3 and 10 minutes, and 39% had a BP drop after 10 minutes(12). A retrospective analysis of 270 participants with OH showed that 43% of patients experienced a BP drop within 3 minutes, and 91% experienced a drop within 30 minutes(13).

2. Pathophysiology and etiology of Orthostatic Hypotension

About 500 to 1,000 ml of blood volume shifts to lower part of the body within 1 min of upright posture and reduce arterial blood pressure. The change stimulate baroreflex that modulates cardiac output and peripheral vessel resistance, which is mediated by central autonomic network, pre and post-ganglionic sympathetic nerves(14, 15). Various etiology of OH has been identified. Neurogenic causes of OH include diseases that can impair vasoconstriction by affecting the central and/or peripheral baroreflex efferent pathway. Common causes of neurogenic OH (NOH) includes neurodegenerative disorders including Parkinson's disease, multiple system atrophy, dementia with Lewy body, and pure autonomic failure. Disorders of peripheral autonomic nerves due to diabetes, amyloids also can cause NOH(16). Recently, antibodies targeting adrenergic or cholinergic receptors was reported to cause neurogenic OH(17). Non-neurogenic causes of OH includes medications or volume deletion, etc.

Several pathophysiological mechanisms have been suggested to explain the delayed BP drop, including increased peripheral venous pooling, increased fluid transudation, or gradual failure of neural and humoral counteraction against redistributed blood volume(12). Progressive decrease in total peripheral resistance(18) or inadequate calf muscle tone(19) was also suggested to be a contributor of delayed OH.

3. Current treatment for Orthostatic Hypotension

Non-pharmacological treatments, including intermittent water bolus and physical counter maneuvers, may alleviate OH-related symptoms but are not sufficient when used alone(20). Pharmacological treatment is essential in managing OH(21).

Midodrine is the first U.S. Food and Drug Administration (FDA)-approved drug that has been shown to improve OH and clinical symptoms in double-blinded placebo-controlled trials(22, 23). This compound is hydrolyzed to its active metabolite, desglymidodrine, that directly activates the alpha1-adrenoreceptors, which increase the peripheral vascular resistance, reduce venous pooling in the legs and splanchnic circulation, and improve orthostatic BP drops(24, 25).

Pyridostigmine is an acetylcholinesterase inhibitor that increases cholinergic signals and facilitates sympathetic ganglionic neurotransmission. Because autonomic ganglionic traffic is minimal in the supine position and is activated with orthostatic pressure, pyridostigmine may increase adrenergic tone only in the upright posture(26). A few short-term studies have reported that pyridostigmine improved DBP drops during standing without aggravation of the supine BP(27, 28).

Atomoxetine is a norepinephrine transporter blocker that increases the norepinephrine concentration in the synaptic gap. It is approved by the FDA for managing attention deficit hyperactivity disorder(29). A few studies reported that low dose atomoxetine (18mg) is effective in OH treatment. When compared with

the midodrine, atomoxetine equally improved orthostatic BP changes. Moreover, atomoxetine improved OH-related symptoms compared with placebo treatment, which was not significant with midodrine treatment(30). However, it is reported to induce hypertension in patients with central autonomic failure with intact peripheral autonomic function(31).

Several randomized clinical trials have evaluated the short-term efficacy and tolerability of midodrine, pyridostigmine, and atomoxetine in patients with OH(10, 21, 27), but the long-term benefits of these pharmacological interventions remain unclear. Moreover, most such trials failed to evaluate these drugs' effects on OH-associated symptoms and HRQOL. Additionally, head-to-head comparisons of these drugs and the probable benefit of combination treatment have not been properly evaluated.

4. **Objectives**

We performed two randomized open-label parallel clinical trial to evaluate the efficacy of medical treatment for NOH, which includes midodrine, pyridostigmine and atomoxetine. First trial was to evaluate long-term (3-month) efficacy and safety of midodrine single, pyridostigmine single, or combination of midodrine and pyridostigmine in patients with classic and delayed OH. Next trial was to evaluate the efficacy and safety of midodrine and atomoxetine in patients with classic OH. We evaluated not only orthostatic BP and heart rate (HR) changes but also associated symptoms, including orthostatic symptoms, depression, and HRQOL. Then, we performed a head-to head comparison of the treatment drugs.

II. Methods

1. Study participants

Patients 18 years or older who visited the Neurology Department of Seoul National University Hospital (SNUH) 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. The OH was defined as a SBP reduction of 20 mmHg or higher or a DBP reduction of 10 mmHg or higher within 3 minutes of standing(32). The exclusion criteria were (1) OH caused by medication, such as diuretics or beta-blockers, (2) taking medications that can interfere with the autonomic nervous system, and (3) a significant systemic illness (exception of those with diabetic autonomic neuropathy). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital. Written informed consent was obtained from all of the participants after a full explanation of the study procedure was provided.

2. Study design

2.1. Midodrine and pyridostigmine trial

We first performed randomized, open-label parallel study regarding single or combined therapy with midodrine and pyridostigmine for classic and delayed

NOH. At baseline, we obtained medical histories, performed physical examinations, and administered self-reported questionnaires. The patients who met the inclusion criteria were than randomized to receive 1 of 3 treatments: (1) midodrine only: 2.5 mg of midodrine twice a day; (2) pyridostigmine only: 30 mg of pyridostigmine twice a day; and (3) midodrine + pyridostigmine: combination of 2.5 mg of midodrine and 30 mg of pyridostigmine twice a day. The dose could be increased to 5 mg of midodrine or 60 mg of pyridostigmine twice a day at the clinician's discretion during follow-up. 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.

2.2. Midodrine and atomoxetine trial

We performed another randomized, open-label parallel study to evaluate efficacy of midodrine and atomoxetine for NOH. Identical baseline and follow-up evaluation was performed for patients who met the inclusion criteria. The patients were randomized to receive either (1) midodrine 5mg twice a day or (2) atomoxetine 18mg once a day. They were evaluated at 1 month after the treatment and those who meets the criteria for OH at one month received combination treatment with both midodrine and atomoxetine. Drug compliance, possible side effects and concomitant medications were checked at each visit.

3. Orthostatic blood pressure measurement

Orthostatic BP and HR were measured after 10 minutes of rest in the supine position using a Welch Allyn BP monitor (Welch Allyn Protocol Inc., Beaverton, OR, USA) and at 1, 3, 5, and 10 minutes after standing. Maximum decrements in SBP and DBP within 3 minutes of standing were recorded. Nadir SBP, DBP, and mean BP (MBP) were recorded, and maximum decrements in SBP and DBP at 3 and 10 minutes were calculated.

4. 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 two components: the OH daily activity scale (OHDAS), which contains 4 items measuring the impact of OH on daily activities, and the OH symptom assessment (OHSA), which contains 6 items measuring the symptoms of OH (dizziness/light headedness, vision disturbance, weakness, fatigue, trouble concentrating, and head/neck discomfort)(33). 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 using the Beck Depression Inventory-II (BDI-II), which comprises 21 multiple-choice questions, each of which can be scored from 0 to 3(34). To assess HRQOL, Short Form (36) Health Survey version 2 (SF-36v2) was administered. SF-36v2 measures eight 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 two summary scales that are normalized to the population (mean=50, standard deviation=10): the physical component summary scale (PCS) and the mental component summary scale (MCS)(35). Better HRQOL is reflected by higher SF-36v2 scores.

5. Study Outcome

The primary end-point was improvement of the orthostatic BP drop at 1 months after treatment. Maximum decrements in SBP and DBP within 3 minutes of standing were analyzed. Secondary end-points were percentage of patients fulfilling OH criteria at 1 and 3 months; improvement of the orthostatic BP drop at 1 month; and amelioration of 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 (CTCAE v 4.0) was used to grade events, and severe adverse events were defined as grade three or more.

6. Statistical analysis

The sizes of groups of participants needed for the first trial was calculated with the software program G*Power(36). According to this program, a total sample size of 81 participants was sufficient to obtain a small effect size of Cohen's f = 0.2 as a result from a repeated measures analysis of variance [ANOVA; within-between interactions; α-level: 0.05, Power (1 − β): 0.95, correlations among repeated measurements: 0.50, Number of group was 3, and number of measurements was 3]. Considering a drop-out rate of 30% the final required sample size was estimated to n=120 patients.

According to the result of the first trial, effect size of Cohen's f was set as moderate (0.3) and a total sample size of 40 participants was sufficient to obtain the power with a repeated measures analysis of variance [ANOVA; within-between interactions; α-level: 0.05, Power (1 − β): 0.95, correlations among repeated measurements: 0.50, Number of group was 2, and number of measurements was 2] for the second trial. Considering a drop-out rate of 20% the final required sample size was estimated to n=50 patients.

All data are presented as the mean±standard deviation (SD). All analysis was 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 using the one-way analysis of variance (ANOVA), and the chi-square test was used to analyze categorical data. Then, we evaluated changes from baseline to 1 month or 3 months after the 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 month and 3 months after treatment) as the within-subject factor was used to test for an overall difference in the treatment effects. Post-hoc analysis was performed using Tukey's 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 using SPSS 22.0 for Windows, and the significance was set at $p<0.05$.

III. Results

1. Participants and Etiology

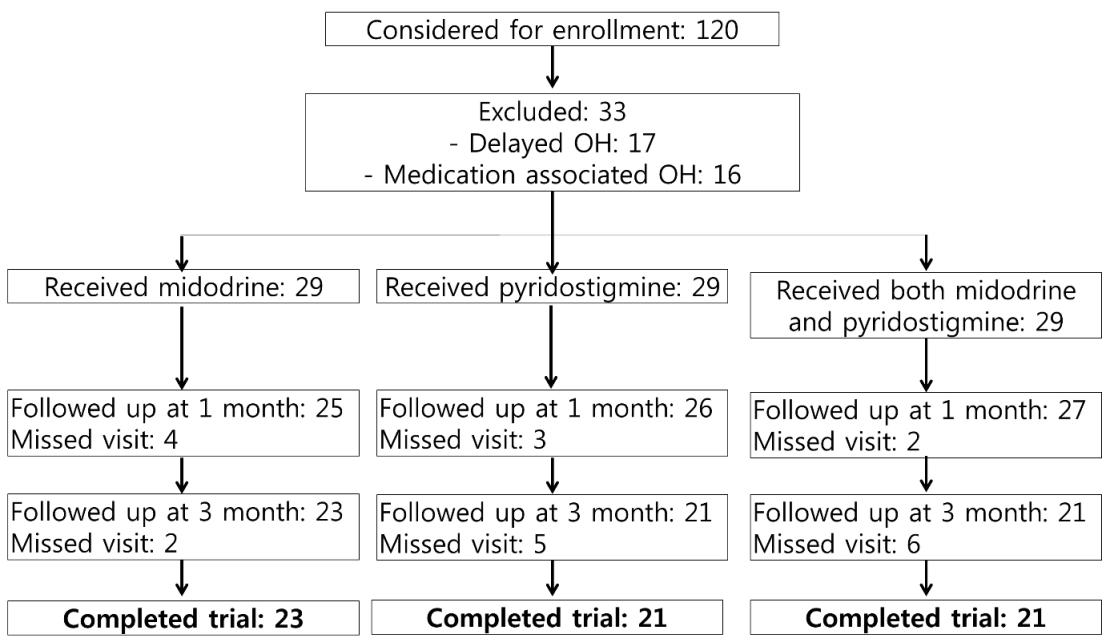
1.1. Midodrine and pyridostigmine trial

The first clinical trial screened 120 patients for inclusion and excluded 16 of them for the use of concomitant drugs that can affect orthostatic BP change. Eighty-seven patients exhibited a decrease in BP within 3 minutes (classic OH) and randomized. (Figure 1) The mean age was 57 years, and 41 (47.1%) were male. The patients were well matched by age and sex. Twenty-three patients had non-diabetic peripheral autonomic neuropathy, 21 patients had diabetic autonomic neuropathy, 4 patients had multiple system atrophy, and 39 patients had unspecified OH (Table 1).

Seventeen other patients were eventually enrolled due to delayed OH. The mean age of the patients with delayed OH was 51.5 years, and 7 (41.2%) were male. The mean body-mass index (BMI) of the patients was 23.2 kg/m2. Baseline characteristics were similar between the patients with delayed and classic OH. Six of them had non-diabetic peripheral autonomic neuropathy, and 11 had an unspecified etiology.

Figure 1. Participant flow of midodrine and pyridostigmine trial.

In total, 120 patients were screened for inclusion in this study and underwent orthostatic BP and HR measurements. Twenty-three patients exhibited a decrease in BP after more than 3 minutes, and 10 patients had OH because of the use of concomitant drugs. Eighty-seven patients were eventually enrolled and were randomized into three groups: midodrine-only, pyridostigmine-only, and midodrine + pyridostigmine groups. Six patients in the midodrine-only group, 8 in the pyridostigmine-only group, and 8 in the midodrine + pyridostigmine group were lost to follow-up.



Abbreviation: OH, orthostatic hypotension

Table 1. Patient characteristics of midodrine and pyridostigmine trial

	Total	Midodrine only	Pyridostigmine only	Midodrine + Pyridostigmine	p-value
	87	29	29	29	
Age (years)	57.2±16.0	59.2±17.7	59.7±13.4	52.7±16.2	0.179
Sex (male)	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	0.74
Weight (kg)	63.0±11.0	62.3±11.0	63.5±10.6	62.3±11.6	0.911
BMI (kg/m2)	25.0±11.9	23.8±3.2	24.2±3.0	27.0±20.2	0.536
Etiology					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; OH, orthostatic hypotension; MSA, multiple system atrophy; PAN, peripheral autonomic neuropathy.
Data are presented as the mean±SD or number (percentage).

1.2. Midodrine and atomoxetine trial

The second clinical trial screened 54 patients for inclusion and excluded 4 of them for concomittant medical conditions or medications. Twenty-five of the patients received midodrine and other 25 received atomoxetine. (Figure 2) Mean age was 63 and 56% were male, which was similar between the two groups. Eight patients (16%) had multiple system atrophy, 8 (16%) had diabetic autonomic neuropathy, 5 (10%) had non-diabetic peripheral autonomic neuropathy, and other 29 (58%) had unspecified etiology. (Table 2.)

Figure 2. Participant flow of midodrine and atomoxetine trial.

In total, 54 patients were screened for inclusion in this study and underwent orthostatic BP and HR measurements. Four patients had OH because of the use of concomitant drugs. Fifty patients were eventually enrolled and were randomized into two groups: midodrine and atomoxetine groups. Three patients in the midodrine group and 6 in the atomoxetine group were lost to follow-up.

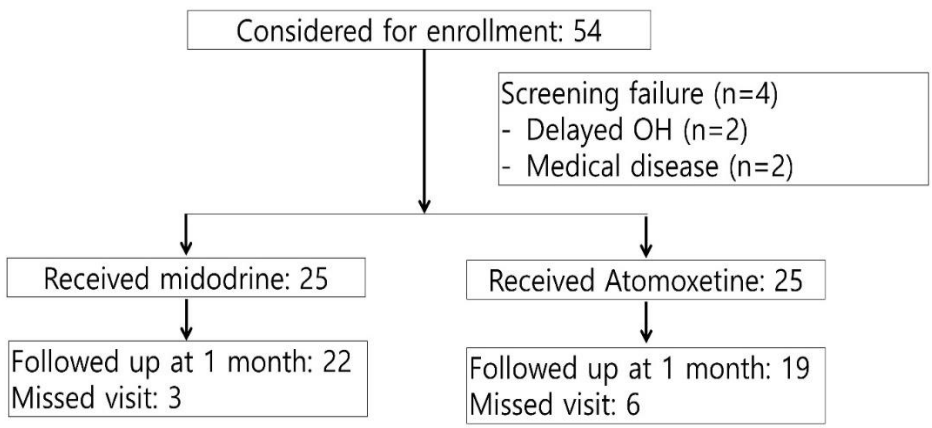


Table 2. Patient characteristics of midodrine and atomoxetine trial

	Total n=50	Midodrine n=25	Atomoxetine n=25	
Age (years)	63.1±9.6	61.8±11.7	64.4±7.0	0.344
Sex (male)	28 (56.0)	14 (56.0)	14 (56.0)	1
Height (cm)	165.0±9.4	164.1±10.7	165.9±8.1	0.514
Weight (kg)	67.5±11.5	67.2±12.0	67.7±11.3	0.876
BMI (kg/m2)	23.7±5.8	23.9±5.7	23.6±6.0	0.876
Etiology				0.799
-Idiopathic OH	29 (58.0)	13 (52.0)	16 (64.0)	
-MSA	8 (16.0)	5 (20.0)	3 (12.0)	
-Diabetic PAN	8 (16.0)	4 (16.0)	4 (16.0)	
-Nondiabetic PAN	5 (10.0)	3 (12.0)	2 (8.0)	

Abbreviations: BMI, body mass index; OH, orthostatic hypotension; MSA, multiple system atrophy; PAN, peripheral autonomic neuropathy.
Data are presented as the mean±SD or number (percentage).

2. Clinical features at Baseline

2.1. Midodrine and pyridostigmine trial (Classic OH)

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 mmHg) and DBP (-14.1±9.0 mmHg) from the supine to the upright position without profound increases in HR (12.9±9.9/min). Orthostatic BP, HR changes, and questionnaire scores, including OHQ, BDI and SF-36v2, were comparable between the groups at baseline.

2.2. Midodrine and pyridostigmine trial (Delayed OH)

Baseline supine vital signs and nadir BP during 10 minutes of standing were similar between those with classic and delayed OH. However, the maximal orthostatic SBP drop within 10 minutes tended to be milder (-20.7±8.8 vs. -25.2±12.1, p=0.081) and the orthostatic DBP drop was smaller (-8.9±8.7 vs -14.7±9.1, p=0.021) in the delayed OH patients.

Questionnaire scores regarding OH-related symptoms were comparable between the classic and delayed OH groups at baseline. The total BDI-II score was similar between the delayed and classic OH patients. Based on the baseline BDI-II score, 35.3% of the patients with delayed OH had mild to moderate depression. However, none of the patients with delayed OH had severe depression, compared with 3.8% of patients in the classic OH group. Deteriorations in physical and mental QOL were found in 14.7% and 35.3% of delayed OH patients, respectively, similar to the findings in classic OH patients. (Table 3.)

Table 3 Patient characteristics between classic and delayed OH

	Delayed OH n=17	Classic OH n=87	p-value*
Age (years)	51.5±16.0	57.2±16.0	0.192
Sex (male)	7 (41.2)	41 (47.1)	0.653
BMI (kg/m^2)	23.2±7.0	25.0±11.9	0.405
Etiology			0.091
Idiopathic OH	11 (64.7)	39 (44.8)	
CNS	0	4 (4.6)	
DM autonomic neuropathy	0	21 (24.1)	
Other autonomic neuropathy	6 (35.3)	23 (26.4)	
Baseline orthostatic vital signs			
Supine SBP, mmHg	130.2±23.6	129.3±18.7	0.973
Supine DBP, mmHg	77.8±10.8	79.4±10.5	0.544
Supine MBP, mmHg	104.4±13.9	104.0±16.5	0.797
Supine HR, mmHg	67.2±11.8	70.2±12.1	0.217
Nadir SBP during 10 min standing, mmHg	105.2±18.6	109.6±21.7	0.452
Nadir DBP during 10 min standing, mmHg	66.1±13.7	68.9±16.2	0.478
Nadir MBP during 10 min standing, mmHg	86.9±15.4	89.7±18.3	0.537
Max 3 min SBP drop, mmHg	-8.5±8.0	-23.5±10.8	**<0.0001**
Max 3 min DBP drop, mmHg	-1.5±4.5	-14.1±9.0	**<0.0001**
Max 3 min HR change, mmHg	12.9±9.9	13.4±7.8	0.814
Max 10 min SBP drop, mmHg	-20.7±8.8	-25.2±12.1	0.081
Max 10 min DBP drop, mmHg	-8.9±8.7	-14.7±9.1	**0.021**
Max 10 min HR change, mmHg	15.6±10.5	16.4±9.5	0.778
Baseline Questionnaires			
OHDAS total score	8.5±6.1	12.4±10.4	0.137
OHSA total score	18.2±9.3	21.0±12.2	0.285
BDI-II total score	11.9±5.0	13.4±7.8	0.316
SF-36, PCS	44.3±8.1	42.0±8.6	0.302
SF-36, MCS	45.6±8.1	43.4±9.0	0.339

Abbreviations: OHDAS, orthostatic hypotension daily activity scale; OHSA, orthostatic hypotension symptom assessment; BDI, Beck depression inventory; SF-36, Short Form 36; PCS, physical component scale; MCS, mental component scale. Data are presented as the means±SD or numbers (percentages). *p-value for the Mann-Whitney U test.

2.3. Midodrine and atomoxetine trial

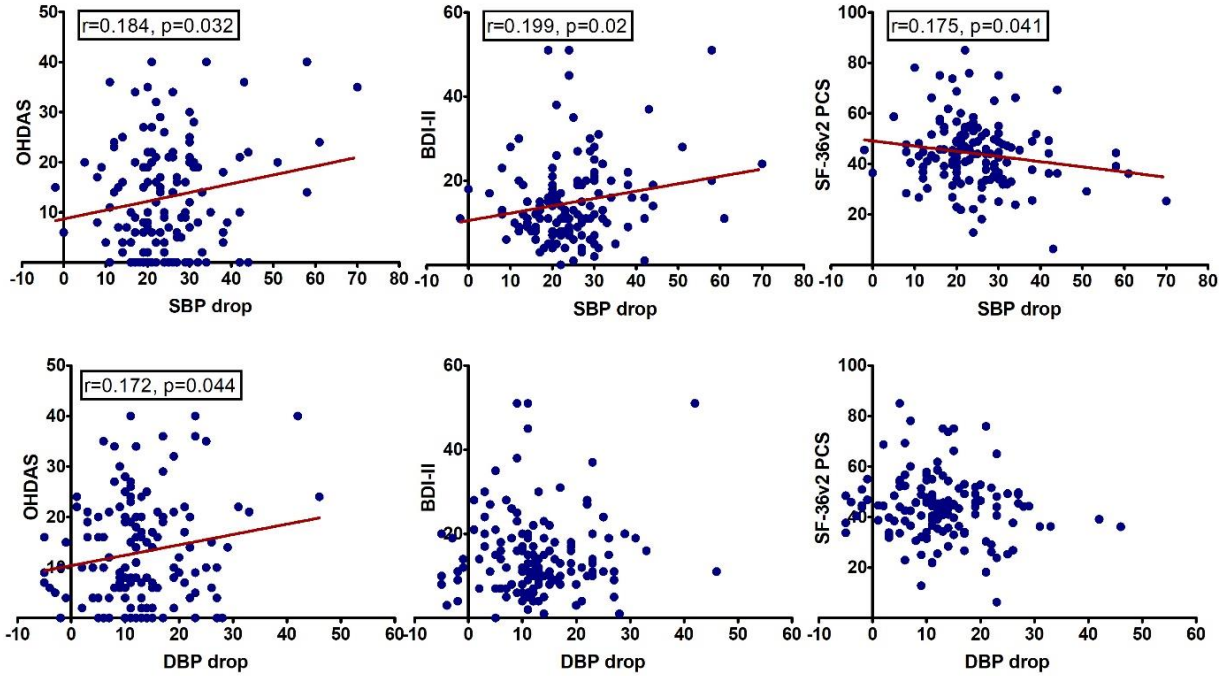
Baseline supine SBP, DBP and MBP were similar between midodrine and atomoxetine treatment groups. Supine HR tended to be higher for the atomoxetine group (71.5±16.4 vs 64.9±7.9, p=0.078). All patients exhibited substantial decreases in SBP (-23.5±10.8 mmHg) and DBP (-14.1±9.0 mmHg) from the supine to the upright position without profound increases in HR (12.9±9.9/min).

Orthostatic BP, HR changes, and questionnaire scores, including OHQ, BDI and SF-36v2, were comparable between the groups at baseline.

2.4. Orthostatic vital signs and symptom severity

Overall, positive correlation was found between SBP drop and OHDAS (r=0.184, p=0.032), BDI (r=0.199, p=0.002), and DBP drop and OHDAS (r=0.172, p=0.044). There was negative correlation between SBP drop and SF-36 PCS (r=-0.175, p=0.041). No significant correlation was found between OH related symptom severity and nadir SBP, DBP or HR. (Figure 3.)

Figure 3. Correlation analysis of orthostatic vital signs and symptom severity.



Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; OHDAS, orthostatic hypotension daily activity scale; BDI-II, Beck Depression Inventory-II; SF-36v2, Short Form (36) Health Survey version 2; PCS, physical component score.

3. Number of patients who met BP criteria for OH

3.1. Midodrine and pyridostigmine trial (Classic OH)

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 42.4% 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, 0.459 respectively). The proportion of patients who met the BP criteria were 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 4). Twenty-one patients were lost to follow-up at 3 months, and demographics, initial supine or orthostatic vital signs or treatment modalities were similar between those who completed the study and those who did not. The results of SF-36v2 were not obtained in 4 patients (one in the midodrine-only group and three in the pyridostigmine-only group), and the BDI was not obtained in one patient in the midodrine-only group.

Table 4. Orthostatic vital signs at baseline and 1 and 3 months after single and combined midodrine and pyridostigmine.

	Total	Midodrine	Pyridostigmine	Midodrine + Pyridostigmine	p-value 1)
No. of patients who meets BP criteria for OH					
Baseline	87	29	29	29	
1 month	37/78 (47.4)	11/25 (44.0)	12/26 (46.2)	14/27 (51.9)	0.841
3 months	28/65 (43.1)	10/23 (43.5)	11/21 (52.4)	7/21 (33.3)	0.459
Orthostatic SBP drop (mmHg)					
Baseline	-23.5±10.8	-24.7±9.9	-23.3±12.5	-22.5±10.1	0.732
1 month	-14.3±16.3†	-12.6±16.4†	-17.4±18.5	-12.9±14.0†	0.498
3 months	-11.9±13.0†	-12.2±12.8†	-11.7±14.7†	-11.9±12.0†	0.990
Orthostatic DBP drop (mmHg)					
Baseline	-14.1±9.0	-13.4±9.0	15.5±9.9	-13.4±8.2	0.59
1 month	-4.1±14.9†	-7.8±16.4	-1.6±14.0†	-3.1±13.6†	0.303
3 months	-5.2±12.3†	-5.0±12.6*	-4.2±13.2*	-6.6±11.5*	0.809
Orthostatic HR change					
Baseline	12.9±9.9	11.9±13.5	13.8±9.1	13.0±5.8	0.783
1 month	13.3±8.1	12.4±7.5	13.6±8.4	13.9±8.7	0.783
3 months	11.2±7.5‡	10.4±4.8	10.7±9.2	12.6±8.1	0.591
Supine SBP (mmHg)					
Baseline	127.9±19.4	137.3±20.9	124.5±18.5	122.0±15.6	0.004
1 month	134.2±19.4†	136.9±18.5	132.5±21.5*	133.3±18.4†	0.701
3 months	132.8±19.6*	131.4±17.3	135.1±22.5*	131.8±19.3†	0.787
Supine DBP (mmHg)					
Baseline	78.9±11.4	83.2±12.8	76.5±9.8	76.9±10.4	0.041
1 month	79.6±15.0	82.7±14.0	76.2±14.7	80.0±16.0	0.297
3 months	77.9±14.0	77.8±12.4	74.1±14.6	81.8±15.0*	0.226
Supine HR					
Baseline	67.2±11.8	68.0±11.3	66.7±13.5	67.0±10.7	0.9
1 month	69.5±11.0*	69.6±11.8	69.5±12.9	69.3±8.3	0.995
3 months	69.5±12.2	69.0±13.2	70.8±12.4	68.6±11.2	0.818

Abbreviations: OH, orthostatic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure, Data are presented as the mean±SD or number (percentage).

1) p-value from one-way ANOVA or chi-square test *: $p<0.05$ compared with the baseline, †: $p<0.01$ compared with the baseline from the paired t-test, ‡: $p<0.05$ compared with the 1 month

3.2. Midodrine and pyridostigmine trial (Delayed OH)

At 1 month post-treatment, 14 of the patients were followed up. Half of them met the BP criteria for overall classic or delayed OH within 10 minutes. Eleven patients were evaluated at 3 months, and six (54.5%) of them met the criteria for the overall OH. The proportion of patients who met the BP criteria for overall OH did not differ between the treatment groups at 1 and 3 months. However, the number of patients with overall OH at 1 month was only one in the midodrine monotherapy (1/4, 25.0%) and combination (1/4, 25.0%) groups, compared with 5 in the pyridostigmine-only group (5/6, 83.3%). (Table 5.)

Table 5. Orthostatic vital signs and questionnaire of patients with delayed OH at baseline and 1 and 3 months of midodrine or pyridostigmine.

	Baseline n=17	1 month n=14	3 months n=11
Number of patients with BP criteria for overall OH	17	7/14 (50.0)	6/11 (54.5)
Max 10 min SBP drop, mmHg	-20.7±8.8	-12.6±9.4**	-9.2±9.8**
Max 10 min DBP drop, mmHg	-8.9±8.7	-5.0±15.0	-4.2±12.5
Nadir SBP during 10 min standing, mmHg	109.6±21.7	118.5±18.8	123.5±15.3*
Nadir DBP during 10 min standing, mmHg	68.9±16.2	69.4±16.8	77.0±11.2*
Nadir MBP during 10 min standing, mmHg	89.7±18.3	99.1±14.6	104.1±12.4*
Supine SBP, mmHg	130.2±23.6	131.6±23.5	131.9±20.7
Supine DBP, mmHg	77.8±10.8	78.4±18.8	81.2±14.2
Supine MBP, mmHg	104.0±16.5	105.0±18.7	106.5±16.6
OHDAS	8.5±6.1	6.8±6.7	5.3±8.1
OHSA	18.2±9.3	15.1±10.8*	10.6±8.1**†
BDI-II	11.9±5.0	8.9±4.3**	5.9±3.8** ††
SF-36, PCS	44.3±8.1	44.7±9.0*	49.2±6.1**
SF-36, MCS	45.6±8.1	47.9±7.7	50.6±6.6

Abbreviations: OH, orthostatic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure; OHDAS, orthostatic hypotension daily activity scale; OHSA, orthostatic hypotension symptom assessment; BDI, Beck depression inventory; SF-36, Short Form 36; PCS, physical component scale; MCS, mental component scale.

Data are presented as the mean±standard deviation or numbers (percentages).

*: $p<0.1$, **: $p<0.05$ compared with the baseline, ††: $p<0.05$ compared with the 1-month follow-up with Mann-Whitney U test.

3.3. Midodrine and atomoxetine trial

At 1 month after treatment, total 36 patients were evaluated. Five of 19 (26.3%) patients who took midodrine and 5 of 17 (29.4%) patients who took atomoxetine met the criteria for classic OH, which was similar between the two groups (p=0.836). (Table 6.)

Table 6. Orthostatic vital signs at baseline and 1 month after single and combined midodrine and atomoxetine.

	Midodrine	Atomoxetine	p-value[1)]
No. of patients with OH			
Baseline	25	25	
1 month	5/19 (26.3)	5/17 (29.4)	
Orthostatic SPB drop (mmHg)			
Baseline	27.5±11.7	25.12.0	0.538
1 month	17.2±18.2**	10.8±10.6**	0.202
Orthostatic DBP drop (mmHg)			
Baseline	12.4±8.0	14.5±10.1	0.509
1 month	2.3±9.7**	3.4±8.4**	0.721
Orthostatic HR change			
Baseline	11.7±6.6	10.4±13.0	0.719
1 month	7.7±5.4*	6.0±5.5	0.349
Supine SBP (mmHg)			
Baseline	132.7±19.9	124.8±17.9	0.217
1 month	133.3±21.7	125.4±15.9	0.215
Supine DBP (mmHg)			
Baseline	80.6±11.4	79.1±12.2	0.714
1 month	79.2±14.6	79.4±12.4	0.962
Supine HR			
Baseline	65.7±8.3	71.9±17.7	0.18
1 month	76.4±11.5**	81.8±14.8*	0.231
Nadir SBP (mmHg)			
Baseline	105.2±23.9	97.2±18.0	0.264
1 month	115.7±24.1	114.6±21.0**	0.879
Nadir DBP (mmHg)			
Baseline	67.8±16.8	63.8±14.9	0.452
1 month	76.1±14.4*	75.7±14.8**	0.944
Max HR			
Baseline	79.5±10.7	82.5±19.7	0.582
1 month	84.1±11.7	88.0±13.0	0.353

Data are presented as the mean±SD or number (percentage).
[1)] p-value from t-test, *: $p<0.05$ compared with the baseline, **: $p<0.01$ compared with the baseline from the paired t-test

4. Orthostatic vital signs at follow-ups

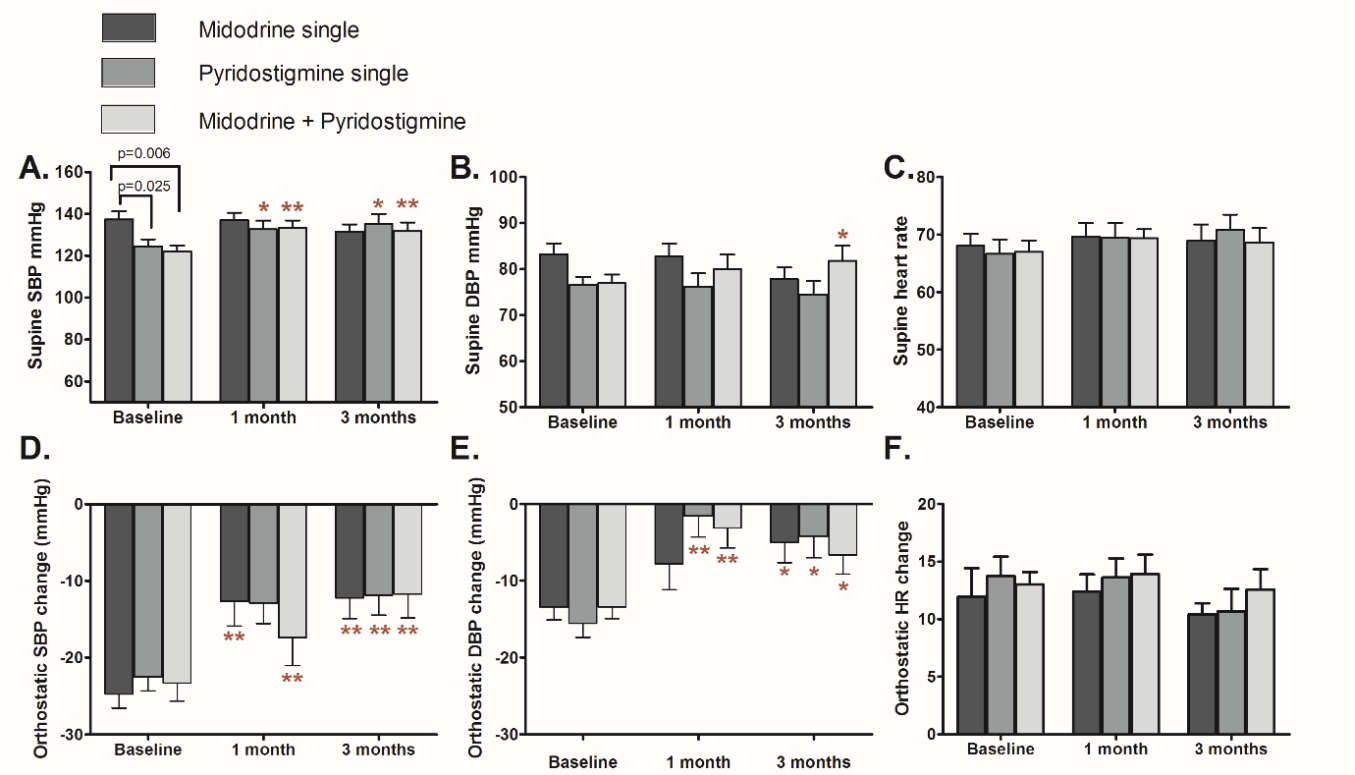
4.1. Midodrine and pyridostigmine trial (Classic OH)

The orthostatic BP drop improved in all treatment groups at 1 and 3 months without significant HR changes. At 1 month after treatment, the midodrine + pyridostigmine group showed significant decreases in both orthostatic SBP and DBP drops. 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 significantly in all treatment groups. No significant difference in the degree of orthostatic BP drop was observed between the groups at 1 month and 3 months.

The supine SBP significantly 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 4 and Table 4).

Repeated-measures ANOVA revealed significant 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 significant group by time interaction [$F(4, 126)=3.308$, $p=0.013$]

Figure 4. Supine and orthostatic vital signs at baseline and 1 and 3 months after midodrine or pyridostigmine.



*: p<0.05 compared with the baseline, **: p<0.01 compared with the baseline from the paired t-test
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

4.2. Midodrine and pyridostigmine trial (Delayed OH)

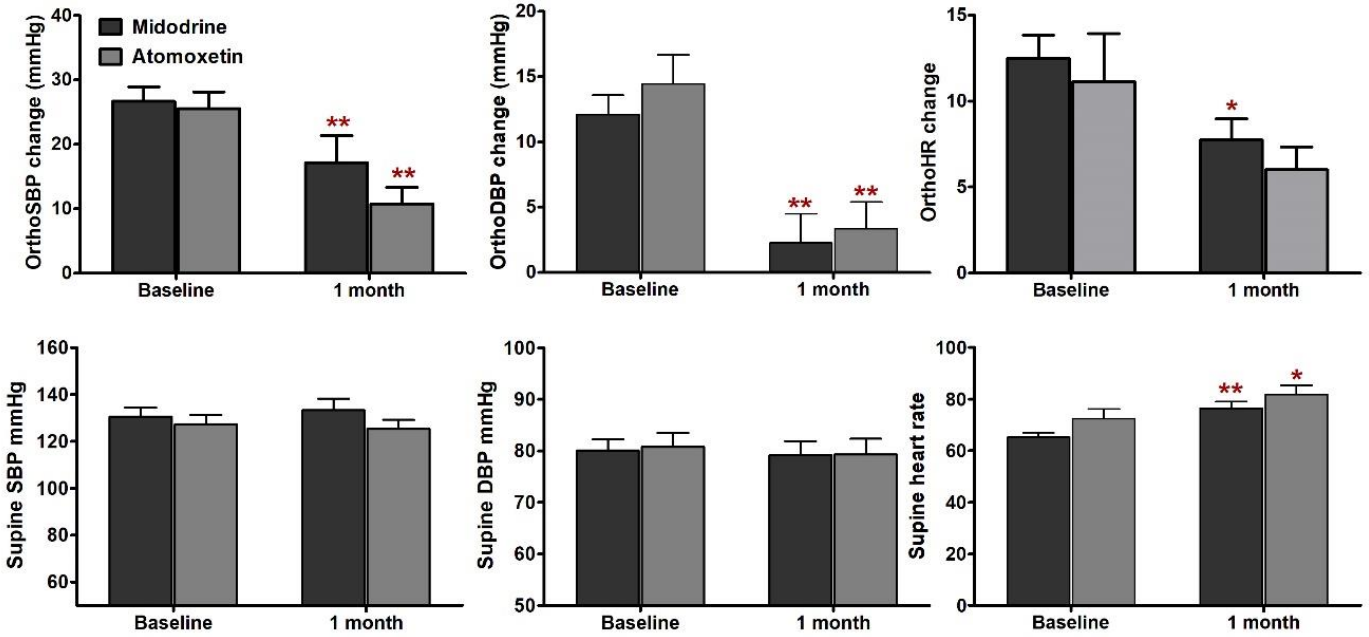
Overall, the orthostatic SBP drop was reduced at 1 and 3 months post-treatment compared with the baseline (p=0.011 for both 1 and 3 months). Nadir SBP (p=0.073), DBP (p=0.058), and MBP (p=0.05) within 10 minutes standing at 3 months tended to be increased compared with the baseline. Supine vital sign measurements showed no significant changes post-treatment. The midodrine-only and combination groups showed a tendency toward improvement in the SBP drop at 1 month (p=0.068 for both the midodrine-only and combination groups). However, the pyridostigmine-only group showed no significant changes in the orthostatic BP drop (p=0.344). The degree of orthostatic SBP drop at 1 month was lower in the midodrine-only group compared with the pyridostigmine-only group (-5.5±5.7 vs -20.2±5.9, post hoc p=0.01).(Table 5.)

4.3. Midodrine and atomoxetine trial

The orthostatic BP drop improved in both midodrine and atomoxetine at 1 month. Orthostatic HR decreased significantly only in midodrine group. Nadir SBP ($p=0.002$), DBP ($p=0.007$), and MBP ($p=0.001$) during 3 minutes of standing increased only in the atomoxetine treatment group. There was no significant change in supine SBP and DBP, however supine HR increased significantly in both treatment groups. (Figure 5, Table 6)

Repeated-measures ANOVA revealed significant time effects on orthostatic SBP drops, DBP drops, HR change, supine HR, nadir SBP, DBP and MBP. No significant effect of the treatment group nor group by time interaction was observed.

Figure 5. Supine vital signs and orthostatic vital signs at baseline and 1 and 3 months after the midodrine or atomoxetine.



*: p<0.05 compared with the baseline, **: p<0.01 compared with the baseline from the paired t-test

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

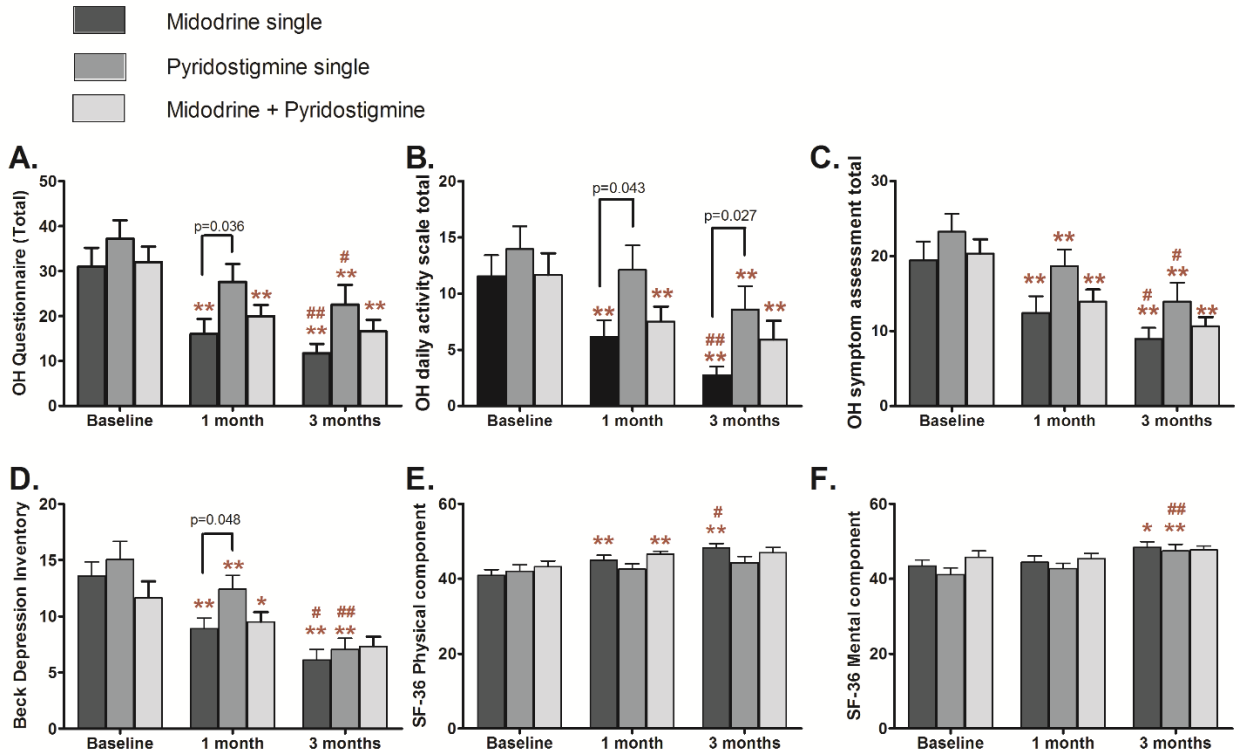
5. Questionnaire scores at follow-up

5.1. Midodrine and pyridostigmine trial (Classic OH)

The midodrine-only group showed lower total OHQ and BDI-II 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. Additionally, the BDI and SF-36v2 MCS scores improved significantly 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, OHSA and BDI scores decreased in the midodrine-only and pyridostigmine-only groups at 3 months but not in the combination group. The use of anti-depressants was similar among the groups at all time points. (Figure 6, Table 7)

Repeated-measures ANOVA analysis revealed significant time effects on all questionnaire scores. A significant 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 significant group by time interaction [$F(4,124)=2.480$, $p=0.047$]. Improvement in BDI score at 1 month was greater in the midodrine single 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, $p=0.047$).

Figure 6. Questionnaire scores at baseline and 1 and 3 months after the midodrine or pyridostigmine



Abbreviation: OHDAS, orthostatic hypotension daily activity scale; OHSA, orthostatic hypotension symptom assessment; SF-36, Short Form 36, *: p<0.05 compared with the baseline, **: p<0.01 compared with the baseline from the paired t-test

Table 7. Questionnaire scores at baseline and 1 and 3 months of single and combined midodrine and pyridostigmine.

	Total	Midodrine	Pyridostigmine	Midodrine + Pyridostigmine	p-value1)
OH Questionnaire total score					
Baseline	33.4±21.0	31.0±22.5	37.2±22.0	32.0±18.6	0.488
1 month	21.2±18.3†	16.0±17.8†	27.6±21.4	20.0±13.8†	0.048
3 months	16.9±15.4†§	11.7±10.1†§	22.6±20.6†	16.5±12.0†	0.058
OHDAS					
Baseline	12.4±10.4	11.6±10.1	14.0±10.9	11.7±10.4	0.613
1 month	8.6±8.9†	6.2±7.4†	12.1±11.1	7.5±6.9†	0.041
3 months	5.7±7.7†§	2.7±3.7†§	8.6±9.6†	5.9±7.8†	0.035
OHSA					
Baseline	21.0±12.2	19.5±13.4	23.2±12.9	20.3±10.3	0.472
1 month	15.0±10.5†	12.4±11.0†	18.7±11.2†	13.9±8.5†	0.081
3 months	11.2±8.7†§	9.0±7.0†‡	14.0±11.6†‡	10.6±5.7†	0.146
BDI					
Baseline	13.4±7.8	13.6±6.8	15.1±8.6	11.7±7.9	0.253
1 month	10.3±5.4†	8.9±4.7†	12.4±6.2†	9.5±4.5*	0.04
3 months	6.9±4.3†§	6.1±4.3†§	7.2±4.7†§	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 month	44.7±6.3†	44.9±6.9†	42.6±7.1	46.5±4.0†	0.068
3 months	46.6±6.7†‡	48.3±5.3†‡	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 month	44.1±7.8	44.4±8.6	42.7±7.3	45.3±7.4	0.458
3 months	47.9±6.7†§	48.4±7.2*	47.4±7.9†§	47.7±5.0	0.892

Abbreviations: OHDAS, orthostatic hypotension daily activity scale; OHSA, orthostatic hypotension symptom assessment; BDI, Beck depression inventory; SF-36, Short Form 36; PCS, physical component scale; MCS, mental component scale.
Data are presented as the mean±SD or number (percentage).

1) p-value from one-way ANOVA or chi-square test *: $p<0.05$ compared with the baseline, †: $p<0.01$ compared with the baseline from the paired t-test

‡: $p<0.05$ compared with 1 month; §: $p<0.01$ compared with 1 month from the paired t-test

5.2. Midodrine and pyridostigmine trial (Delayed OH)

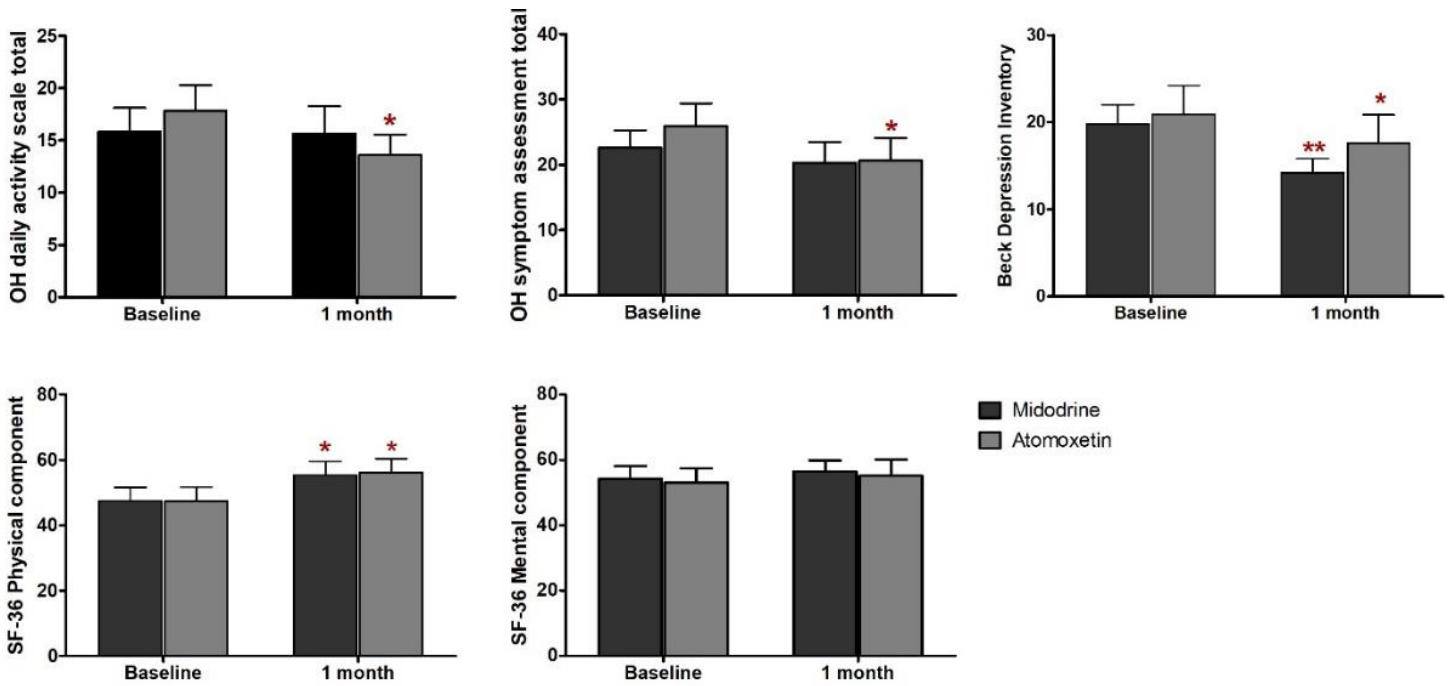
Overall, the BDI-II score improved at 1 and 3 months after the treatment (p=0.009 and 0.019, respectively), and the OHSA score decreased at 3 months (p=0.023) compared with that measured at baseline. The SF-36v2 PCS score improved at 3 months compared with that at 1 month. (Table 5)

5.3. Midodrine and atomoxetine trial

OHDAS and OHSA score improved significantly only in atomoxetine group at 1 month of treatment, but not in midodrine group. BDI and SF-36 PCS scores improved significantly in both midodrine and atomoxetine group. (Figure 7, Table 8)

Repeated-measures ANOVA analysis revealed significant time effects on all questionnaire scores except for SF-36 MCS score. Only OHDAS score had a significant group by time interaction [F (1,34)=4.454, p=0.042].

Figure 7. Questionnaire scores at baseline and 1 month after the midodrine or atomoxetine.



Abbreviation: OHDAS, orthostatic hypotension daily activity scale; OHSA, orthostatic hypotension symptom assessment; SF-36, Short Form 36

*: $p<0.05$ compared with the baseline, **: $p<0.01$ compared with the baseline from the paired t-test

Table 8. Questionnaire scores at baseline and 1 month of midodrine and atomoxetine.

	Midodrine	Atomoxetine	p-value[1)]
OHDAS			
Baseline	15.6±11.2	19.1±11.5	0.366
1 month	15.6±11.6	13.6±8.1*	0.54
OHSA			
Baseline	21.5±13.0	26.6±16.5	0.319
1 month	20.3±13.8	20.7±14.2*	0.944
BDI-2			
Baseline	18.7±7.4	21.2±15.9	0.534
1 month	14.2±6.9**	17.6±13.4*	0.358
SF-36v2, Physical component			
Baseline	49.7±18.5	47.0±20.1	0.689
1 month	55.4±18.2*	56.3±17.2*	0.884
SF-36v2, Mental component			
Baseline	56.3±17.1	53.1±20.0	0.616
1 month	56.4±14.8	55.1±20.8	0.827

Abbreviations: OHDAS, orthostatic hypotension daily activity scale; OHSA, orthostatic hypotension symptom assessment; BDI, Beck depression inventory; SF-36, Short Form 36; PCS, physical component scale; MCS, mental component scale.
Data are presented as the mean±SD or number (percentage).
[1)] p-value from t-test, *: $p<0.05$ compared with the baseline, **: $p<0.01$ compared with the baseline from the paired t-test

6. Predictors of treatment response.

We evaluated whether the treatment response differed according to etiology of OH. No significant difference was found in proportion of patients who meets the criteria for OH at 1 month, and degree of orthostatic BP or questionnaire score improvement between the etiologies. To evaluate whether improvement in orthostatic BP was associated with amelioration of the associated symptoms, we evaluated the correlation between changes in orthostatic BP drop within 1 months of treatment and the degree of improvement in the questionnaire scores. No significant association was observed only between orthostatic BP drop and improvement in any questionnaire scores.

7. Adverse events

7.1. Midodrine and pyridostigmine trial (Classic OH)

Ten (10/87, 11.5%) of the patients reported adverse events, and the proportion did not differ between the treatment modalities (p=0.111). All adverse events occurred within 1 month and were grade one or two (mild to moderate) in severity. One patient in the midodrine-only group (4.3%) reported headache and aggravated dizziness. Six patients in the pyridostigmine-only group (25.0%) reported aggravated dizziness (n=5); headache (n=2); gastrointestinal (GI) 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 (4/87, 4.6%) of the patients (2 patients in the pyridostigmine-only group and 2 patients in the midodrine + pyridostigmine group) discontinued or changed the treatment because of the side effects (GI symptoms or dizziness); the other adverse effects resolved spontaneously.

7.2. Midodrine and atomoxetine trial

Two (2/50, 4.0%) of the patients reported adverse events; one who received midodrine and the other received atomoxetine. All adverse events occurred within 1 month and were grade one or two (mild to moderate) in severity. One patient in the midodrine group suffered neck stiffness and headache after the treatment. The other in the atomoxetine group suffered nausea and anorexia, which improved after cessation of the medication.

IV. Discussion

1. Summary

Midodrine, pyridostigmine, and atomoxetine significantly improved orthostatic BP changes and associated symptoms at 1 month after treatment. Less than half of the patients met the BP criteria for OH at 1 month after the treatment. Overall, improvement in BP drop were comparable between midodrine, pyridostigmine and atomoxetine. Midodrine was better at ameliorating OH-associated symptoms than pyridostigmine. Atomoxetine was even better at improving OHDAS score than the midodrine. The combination of the midodrine and atomoxetine demonstrated beneficial effects in controlling orthostatic BP drops but failed to show better improvement in OH-related symptoms. Patients with delayed OH, despite having less of an orthostatic BP drop, have a similar severity of orthostatic intolerance as those with classic OH. Overall depressive symptoms and HRQOL were also comparable between the classic and delayed OH groups. Standing BP drop and associated symptoms also improved in patients with delayed OH with the midodrine or pyridostigmine. This study was the first to evaluate long-term efficacy and safety of midodrine, pyridostigmine, or atomoxetine.

2. Etiology of OH and clinical symptoms.

Overall, about half of the patients enrolled had idiopathic OH, followed by non-diabetic peripheral autonomic neuropathy, diabetic autonomic neuropathy, and central autonomic disorders. Delayed OH has been regarded as a milder form of classic OH based on the degrees of orthostatic BP drop and autonomic dysfunction(12). In accordance with the previous study(12), the orthostatic BP drop, especially the orthostatic DBP change, was lower in our patients. However, the severity of orthostatic intolerance was not "milder" in delayed OH. Both the OHDAS and OHSA scores were similar between the delayed and classic OH groups. It has been reported that the prevalence of the orthostatic intolerance was similar, regardless of the magnitude and timing of the BP drop(12).

Despite the lower orthostatic BP drop, the nadir BP values during 10 minutes of standing were similar between the classic and delayed OH groups. The result of this study supports the hypothesis that the orthostatic symptoms are more associated with how low the BP falls than with the magnitude of the fall(37). In delayed OH, the symptoms may appear later than after 3 minutes of standing(38); however, the presence of symptoms may determine the perceived severity. Measures of mental- and health-related quality of life were also comparable between the delayed and classic OH groups. Classic OH is known to cause severe impairment in a patient's QOL due to the disabling symptoms of autonomic dysfunction(39). Those with delayed OH also had reduced QOL and had disabling symptoms similar to those with classic OH, which warrants treatment for delayed OH.

3. Efficacy of medical treatment on orthostatic vital signs

3.1. Midodrine and pyridostigmine trial (Classic OH)

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(27). Our study suggests that pyridostigmine alone can 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 the standing SBP(40) and that pyridostigmine affects the standing DBP more strongly(27); however, the mechanism underlying this difference remains unclear. In the combination group, unlike the single-drug treatment groups, which contained similar proportions of OH between 1 and 3 months, the proportion decreased at 3 months relative to that at 1 month.

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 month and 3 months. Because pyridostigmine can cause intermittent

sympathetic hyperactivation(26), its long-term use can increase supine SBP, as suggested in a previous case report(41). 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 the treatment groups.

3.2. Midodrine and pyridostigmine trial (Delayed OH)

Medical treatment with midodrine and/or pyridostigmine in patients with delayed OH reduced orthostatic BP drops. The efficacy of medical treatment for delayed OH has been reported only in a small number of studies. The first study of delayed OH by Streeten and Anderson reported considerable symptom reduction or complete correction with fludrocortisone or octreotide(42). Treatment with sodium chloride for 8 weeks improved orthostatic symptoms and abnormal BP responses during tilt-table testing in half of the patients with delayed OH who presented with chronic fatigue syndrome(43).

Seven of the 14 patients with delayed OH who was followed up at 1 month and 6 of the 11 patients who were followed up at 3 months met the BP criteria for OH. Among those with OH during follow-up, 42.9% and 54.5% met the criteria for classic OH at 1 and 3 months, respectively. A ten-year follow-up study showed that 54% of the patients with delayed OH eventually developed classic OH, and 31% develop an alpha-synucleinopathy. Half of those who progressed to classic OH died within 10 years.(44) However, the substantial portion of classic OH during the follow-up period in the current

study may have resulted from the day-to-day intra-individual variability of blood pressure(45, 46). Puisieux et al. demonstrated that among the 61 patients who met the BP criteria for OH, only 17 fulfilled the criteria when measurements were performed at a different time of day(47).

3.3. Midodrine and atomoxetine trial

Atomoxetine improved standing SBP and DBP drop comparable to those who received midodrine treatment, which was comparable to previous short-term study(30). Atomoxetine blocks the norepinephrine reuptake and increases norepinephrine synaptic concentration and porentiate peripheral sympathetic neurons(48). Therefore intact peripheral noradrenergic autonomic nerves function may be essential for the atomoxetine to show efficacy. Central inhibition of the sympathetic nervous system has been a concern in using atomoxetine in peripheral autonomic disorders, because it can counteract pressor effect of the drug(49). Previous study reported that only patients with central autonomic failure, but not in those with peripheral autonomic failure exhibited standing systolic blood pressure increase after 1hr of atomoxetine(31). We did not performed a subgroup analysis according to its etiology because our study included a large number of patients without definite OH etiology. However, we found reduction in both orthostatic SBP and DBP drop after 1 month use of atomoxetine. Long-term effect of atomoxetine has not been evaluated. Only one case study reported 8 weeks beneficial effect of atomoxetine in elderly patients with idiopathic OH(50). Orthostatic HR change was decreased after 1month only in midodrine group, which was also

shown in the previous study(30). Atomoxetine may also stimulate β1 adrenergic receptors in the heart indirectly by increasing plasma norepinephrine in the synapse(51).

4. Efficacy of medical treatment on associated symptoms

4.1. Midodrine and pyridostigmine trial (Classic OH)

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 that of the control(10). 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(26, 28). One study evaluated symptom improvement at 1 hour after pyridostigmine treatment(26), whereas another reported no significant improvement in presyncopal symptoms(28). Our study revealed that pyridostigmine was less effective at controlling OH symptoms than midodrine. Additionally, a significant group effect on the OHQ and OHDA scores was observed, as follows: midodrine only > midodrine + pyridostigmine > pyridostigmine only. Because pyridostigmine can affect the central nervous system and cause depressed mood, lethargy, and sleep disturbances(52), it may be responsible for the decreases in the subjective symptom scores.

Pharmacological 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 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.

4.2. Midodrine and pyridostigmine trial (Delayed OH)

Medical treatment with midodrine and/or pyridostigmine in patients with delayed OH reduced orthostatic BP drops and improved OH-related symptoms and depression. Specifically, the treatment significantly reduced orthostatic SBP drops and improved OHSA and BDI-II scores at 1 and 3 months. A consensus on whether medical treatment should be used in delayed OH has not yet been established. However, because patients with delayed OH suffer similar orthostatic intolerance to classic OH patients, medical treatment may also be warranted in those patients.

4.3. Midodrine and atomoxetine trial

Improvement of OHDAS and OHSA was significant only in atomoxetine treatment group, but not in midodrine, which was comparable with the previous short-term study(30). Orthostatic intolerance may result from decrease in cerebral blood flow during standing. Atomoxetine may improve cerebral blood flow not by improving systemic blood pressure, but also by direct modulation of cerebral blood flow(53). Compared to our first trial, the midodrine group showed little efficacy in improving OH-related symptoms. Those enrolled in second clinical trial had more central autonomic dysfunction, more severe depression, which may affected the result. We also found improvement in depression and HRQOL in both midodrine and atomoxetine treatment.

5. Limitations

Although this study lacked a blinding process, it must be acknowledged that this work represents the longest study with a randomized design to evaluate the long-term efficacy of midodrine, pyridostigmine and atomoxetine. Compared with previous studies (23, 28, 40, 41), which focused on primary autonomic degenerative disorders, our study included more patients with peripheral autonomic neuropathy. Because our study did not have a placebo group for comparison, placebo and Hawthorne effects cannot be excluded. However, the primary outcome of this study was BP drop, which is an objective measure.

V. Conclusion

Midodrine, pyridostigmine, and atomoxetine improved orthostatic BP drop without severe adverse events. The short-term use of atomoxetine, long-term use of midodrine may be an optimal strategy for managing patients with severe OH related symptoms. 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 pharmacological treatment for OH. Patients with delayed OH also showed similar orthostatic intolerance symptoms despite a lower degree of orthostatic BP drop than those with classic OH. This study suggests that medical treatment with midodrine may be of benefit for the rapid amelioration of symptoms associated with delayed OH.

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요약 (국문초록)

서론: 기립성 저혈압의 치료에서 미도드린은 주요 치료약물이며, 피리도스티그민과 아토목세틴은 임상에서 흔히 사용되고 있다. 하지만 이 약물의 장기사용에 따른 효과와 안정성은 아직 부족하다. 더구나 각각의 약물에 대한 비교연구와 병용사용이 효과적인지에 대한 연구도 아직 없는 실정이다. 본 연구에서 각 약물의 장기간 사용의 효과와 안정성을 평가하고자 한다.

방법: 본 연구는 2 개의 전향적 open-label 무작위 배정 임상시험연구로 증상이 있는 신경인성 기립성저혈압 환자를 등록하였다. 첫 임상시험에서는 1:1:1 비율로 (1) 미도드린 5mg/일; (2) 피리도스티그민 60mg/일; (3) 미도드린 5mg/일 + 피리도스티그민 60mg/일을 무작위로 배정하였다. 또한 후속연구로 지연성 기립성 저혈압 환자에서 미도드린과 피리도스티그민의 효과를 평가하였다. 두번째 임상시험은 (1) 미도드린 5mg 하루 두 번; (2) 아토목세틴 18mg 하루 한 번을 복용하도록 두 그룹으로 무작위배정하였음. 무작위배정은 컴퓨터 무작위 번호추출을 이용하였으며 환자는 1 개월, 3 개월 째 추적검사 시행하였다. 주요평가지표는 1, 3 개월째 기립성 혈압저하였으며, 이차평가지표는 기립성 저혈압 증상 평가 설문지 점수 변화였다. 안전성은 부작용발생을 평가하였으며 intention-to-treat 방법으로 분석하였다.

결과: 첫 임상연구에서 120명의 환자를 모집하였으며 그 중 87명 환자가 무작위 배정되었다. 기립성 혈압저하는 모든 그룹에서 3 개월째 유의미하게 호전되었으며 평균 혈압변화는 그룹간 차이가 없었다. 기립성 증상은 3 개월 치료간 유의하게 감소되었으며 그 정도는 미도드린 > 미도드린+피리도스티그민 > 피리도스티그민 순이었다. 경도에서 중등도의 부작용이 11.5%의 환자에서 보고되었다. 후속 연구에서 지연성 기립성 저혈압 환자의 증상은 전형적 기립성저혈압 환자와 유사하였으며, 치료 3 개월 후 증상이 유의하게 호전됨을 알 수 있었다. 두 번째 임상시험에서 총 54 명의 환자를 스크린하였으며 그 중 50 명 환자가 미도드린 또는 아토목세틴 군으로 무작위배정되었다. 기립성 혈압저하는 치료 1 개월 째 유의하게 호전되었으며 양 군간 차이는 없었다. 기립성

증상은 아토목세틴 치료군에서만 호전되었으며, 우울증, 삶의 질은 양 군에서 모두 호전되었다. 경도에서 중등도의 부작용이 4.0%의 환자에서 보고되었다.

결론: 미도드린, 피리도스티그민, 그리고 아토목세틴은 모두 신경인성 기립성저혈압에서 효과가 있었으며 안전하였다. 미도드린은 피리도스티그민보다, 그리고 아토목세틴은 미도드린보다 기립성저혈압 연관 증상을 호전시키는데 우월하였다. 또한 병용치료는 기립성 혈압변화를 호전시키는데 우월하였으나 증상호전효과는 경미하였다.

주요어: 기립성 저혈압, 미도드린, 피리도스티그민, 아토목세틴, 효과

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