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# Delayed orthostatic hypotension: Severity of clinical symptoms and response to medical treatment

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ABSTRACT

*Introduction:* Severity of orthostatic intolerance and the benefit of medical treatment in patients with delayed OH have not been elucidated. This study aimed to compare the symptom severity between classic and delayed OH and evaluate the efficacy of midodrine or pyridostigmine in patients with delayed OH.

*Methods:* This was an adjunctive study of previously reported randomized, open-label clinical trials evaluating the efficacy and safety of midodrine or pyridostigmine for classic OH. Seventeen patients with delayed OH were enrolled and also received midodrine (2.5 mg twice a day) or pyridostigmine (30 mg twice a day) alone or combined. Result of initial orthostatic vital sign and questionnaires were compared between the patients with delayed OH and previously reported 87 patients with classic OH. Delayed OH patients were followed up at 1 and 3 months post-treatment and the vital sign measurements and questionnaires were repeated during the follow-up period.

*Results:* Questionnaire scores regarding OH-related symptoms, depression and health-related quality of life (HRQOL) were comparable between the classic and delayed OH patients at baseline. OH-related symptoms and depression were significantly improved after 3 months of medical treatment.

*Conclusion:* Patients with delayed OH exhibited orthostatic intolerance similar to that of classic OH. This study shows that these patients may benefit from medical treatment with either midodrine or pyridostigmine.

## 1. Introduction

"Classic" orthostatic hypotension (OH) is defined as 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 min of standing or upright tilt table testing to 60° (Freeman et al., 2011). However, the blood pressure (BP) drop commonly occurs beyond 3 min; when this occurs, it is referred to as delayed OH. OH can be clinically classified into several categories, and delayed OH is recognized as a potential etiology of orthostatic intolerance (Freeman et al., 2011; Cheshire Jr, 2017).

Among 230 patients with orthostatic intolerance enrolled in a previous study, less than half (46%) exhibited a BP drop within 3 min, 15% had a BP drop between 3 and 10 min, and 39% had a BP drop after 10 min (Gibbons and Freeman, 2006). A retrospective analysis of 270 participants with OH showed that 43% of patients experienced a BP drop within 3 min, and 91% experienced a drop within 30 min

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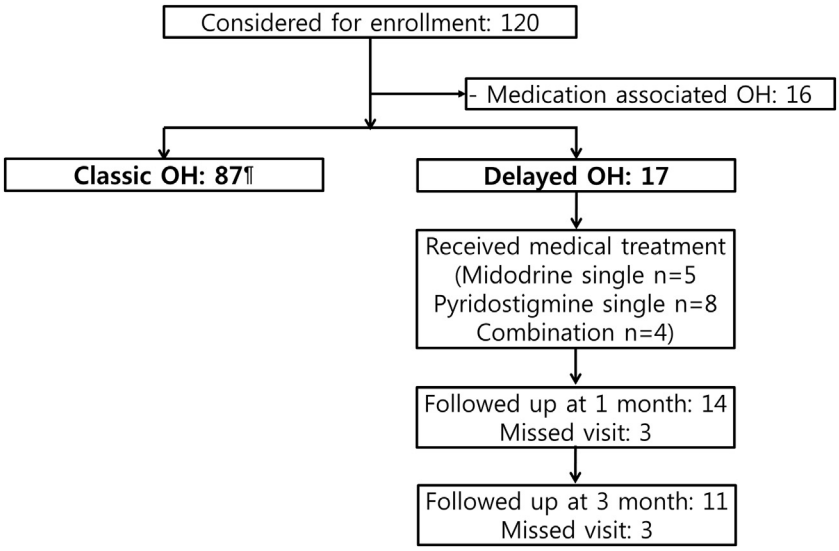


**Fig. 1.** Participant flow chart.
Among the 120 patients who were screened for inclusion in this study and underwent orthostatic BP and HR measurements, 16 patients were excluded due to the use of concomitant drugs. Eighty-seven patients exhibited a decrease in BP within 3 min (classic OH), and their data were published in "Efficacy of single or combined midodrine and pyridostigmine in orthostatic hypotension" (Byun et al., 2017). Seventeen patients were eventually enrolled due to delayed OH.
Abbreviation: OH, orthostatic hypotension

(Gurevich et al., 2014).

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 (Gibbons and Freeman, 2006). Progressive decrease in total peripheral resistance (Podoleanu et al., 2009) or inadequate calf muscle tone (Madhavan et al., 2008) was also suggested to be a contributor of delayed OH. A recent report suggests that delayed OH is an earlier, milder form of classic OH (Gibbons and Freeman, 2015) based on milder sympathetic adrenergic dysfunction during the Valsalva maneuver (Gibbons and Freeman, 2006).

Evaluation of patients with delayed OH has focused primarily on their orthostatic BP or heart rate (HR) changes or on laboratory autonomic function test results. Although the main reason for a clinic visit in these patients is orthostatic intolerance, its impact on quality of life has not been evaluated in detail. Whether delayed OH can reduce health-related quality of life (HRQOL) or cause depression is unclear. Moreover, the necessity of medical treatment that is known to improve orthostatic BP changes and associated symptoms in classic OH (Singer et al., 2006; Byun et al., 2017), including midodrine and pyridostigmine, has not been properly evaluated in delayed OH.

Delayed OH can cause hypotensive symptoms, such as dizziness, pre-syncope, weakness, fatigue, and palpitation (Streeten and Anderson Jr., 1992). Fatigue was even more common in patients with delayed OH than in those with classic OH. We hypothesized that the patients with delayed OH may also have similar disturbances as classic OH, which can be relieved after medical treatment. Therefore, we first performed a cross-sectional study to assess OH-related symptom severity in delayed OH and to compare it with that of classic OH. Then, we performed an observational study to evaluate the efficacy of treatment with midodrine and pyridostigmine for up to 3 months in patients with delayed OH.

## 2. Methods

### 2.1. Study participants and ethics

This was an adjunctive study of a randomized, open-label clinical trial of midodrine and pyridostigmine for OH, which was registered at ClinicalTrials.gov (NCT02308124) (Byun et al., 2017). Previously, we enrolled 120 consecutive patients with symptomatic OH within 10 min of standing and reported the medical treatment outcome in 87 of those with classic OH (Byun et al., 2017). This study analyzed 17 of the patients who were excluded for having delayed OH, which was defined as a SBP reduction of 20 mmHg or higher or a DBP reduction of 10 mmHg or higher after 3 to 10 min of standing. Those with (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) were excluded. Patients with typical history with prodromes and triggers of vasovagal syncope were excluded after clinical interview by neurology experts (K·C, J.I·B). This study was approved by the Institutional Review Board (IRB) of SNUH (IRB No: 1409-066-609). Written informed consent to participate was obtained from all enrolled patients.

### 2.2. Study design and procedures

We first performed a cross-sectional study comparing orthostatic BP changes and symptom severity between classic and delayed OH. In addition, we performed an observational study to evaluate the effects of midodrine or pyridostigmine on BP changes and symptom severity for up to 3 months in patients with delayed OH. Patients rested in a supine position for 10 min and then actively stood in the upright position for 10 min. Orthostatic BP and HR were measured 1, 3, 5, and 10 min after standing, as stated previously (Byun et al., 2017). Nadir SBP, DBP, and mean BP (MBP) were recorded, and maximum decrements in SBP and DBP at 3 and 10 min were calculated. The patients with delayed OH were excluded from the previous study but also received medical treatment with either midodrine (2.5 mg twice a day) or pyridostigmine (30 mg twice a day) as monotherapy or combination therapy based on the treating physician's preference and acceptance of the treatment by the patient, and they were followed for up to 3 months. Five of the patients with delayed OH received midodrine only, 8 of them received pyridostigmine only, and the rest received a combination of midodrine and pyridostigmine (Fig. 1). The patients also received education for non-pharmacological measures for orthostatic hypotension (e.g., increased water intake, high-salt diet, isometric exercises, and other measures).

The orthostatic BP and HR measurements, along with the questionnaires, were repeated at 1 and 3 months post-treatment. Three sets of self-reported questionnaires were administered: OH questionnaire (OHQ) (Kaufmann et al., 2012), the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), and HRQOL using the Short Form (36) Health Survey version 2 (SF-36v2) (Kim et al., 2013). Two components of the OHQ were analyzed: the OH daily activity scale (OHDAS) and the OH symptom assessment (OHSA). The OHDAS contains 4 items measuring