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Editorial Board Member of *World Journal of Clinical Cases*, Jie-Feng Huang, PhD, Associate Chief Physician, Associate Professor, Department of Orthopaedics and Traumatology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang Province, China. 40983285@qq.com

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effects of Kampo medicine hangebyakujutsutemmato on persistent postural-perceptual dizziness: A retrospective pilot study

Toru Miwa, Shin-ichi Kanemaru

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Toru Miwa, Department of Otolaryngology-Head and Neck Surgery, Osaka Metropolitan University, Osaka 5458585, Japan

Toru Miwa, Shin-ichi Kanemaru, Department of Otolaryngology-Head and Neck Surgery, Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka 5308480, Japan

Toru Miwa, Shin-ichi Kanemaru, Department of Otolaryngology-Head and Neck Surgery, Kyoto University, Kyoto 7507501, Japan

Corresponding author: Toru Miwa, MD, PhD, Neurosurgeon, Research Scientist, Department of Otolaryngology-Head and Neck Surgery, Osaka Metropolitan University, 1-4-3 Asahi-cho, Abeno-ku, Osaka 5458585, Japan. miw.com1101@gmail.com

Abstract

BACKGROUND

Persistent postural-perceptual dizziness (PPPD) is a functional disorder, typically preceded by acute vestibular disorders. It is characterized by a shift in processing spatial orientation information, to favor visual over vestibular and somatosensory inputs, and a failure of higher cortical mechanisms. To date, no therapies for PPPD have been approved. Kampo medicine hangebyakujutsutemmato (HBT) has been reported to alleviate disturbances of equilibrium. We hypothesized that HBT would be a beneficial treatment for PPPD.

AIM

To examine the efficacy of HBT for the treatment of PPPD.

METHODS

Patients with PPPD were enrolled and divided into two groups: The HBT group (n = 24) and the non-HBT group (n = 14). The participants completed questionnaire surveys [Niigata PPPD questionnaire (NPQ), dizziness handicap inventory, hospital anxiety and depression scale (HADS), orthostatic dysregulation questionnaire, pittsburg sleep quality index (PSQI), and motion sickness scores] before and after HBT treatment. Additionally, to identify HBT responders, multivariate regression analysis was performed using the results of the ques-tionnaire surveys and equilibrium tests; including stabilometry, and caloric, vestibular evoked myogenic response, and head-up tilt tests.

RESULTS

Thirty-eight outpatients were included in this study, of which 14 patients (3 men, 11 women; mean age, 63.5 ± 15.9 years) received treatment without HBT, and 24 (1 man, 23 women; mean age, 58.2 ± 18.7 years) received combination treatment with HBT. Following HBT treatment, NPQ scores decreased significantly (baseline 40.1 ± 10.0 *vs* 2 mo 24.6 ± 17.7, $P < 0.001$). No statistically significant changes were observed in the NPQ scores in the non-HBT group (baseline 38.6 ± 12.2 *vs* 2 mo 39.4 ± 14.4, $P = 0.92$). Multivariable regression analysis revealed that the results of stabilometry ($P = 0.02$) and the caloric ($P = 0.03$), and head-up tilt tests ($P < 0.001$), HADS ($P = 0.003$), and PSQI ($P = 0.01$) were associated with HBT responsiveness in PPPD patients.

CONCLUSION

HBT may be an effective adjunct therapy for PPPD. Patients with autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality may be high responders to HBT.

Key Words: Hangebyakujutsutemmato; Kampo medicine; Persistent postural-perceptual dizziness; Niigata persistent postural-perceptual dizziness questionnaire score; Sensory reweighting; Treatment responder

Core Tip: Persistent postural-perceptual dizziness (PPPD) is characterized by a shift in processing spatial orientation information to favor visual or somatosensory information over vestibular inputs, as well as failure of higher cortical mechanisms. Our retrospective study showed that Kampo medicine Hangebyakujutsutemmato (HBT) was effective as an adjunctive therapy for PPPD. Additionally, HBT responders had baseline autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality. According to our results, and previous reports, several herbal ingredients in HBT might improve autonomic function and the cyclic AMP response element binding protein/the brain-derived neurotrophic factor pathway, resulting in sensory reweighting to establish a balance between the systems involved in PPPD.

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INTRODUCTION

Persistent postural-perceptual dizziness (PPPD) is a novel disorder characterized by functional dizziness, but it is neither a structural nor a psychiatric condition. PPPD supersedes phobic postural vertigo (PPV) and chronic subjective dizziness (CSD) and is characterized by a persistent chronic vestibular syndrome lasting > 3 mo that is typically preceded by acute vestibular disorders[1]. The core vestibular symptoms of PPPD are dizziness, unsteadiness, or non-spinning vertigo, which are exacerbated by an upright posture/walking, active or passive movement, and exposure to movement or complex visual stimuli[1]. The presence of three exacerbating factors is a characteristic of PPPD[1]. No specific laboratory test for PPPD is available, and the precise assessment of symptoms, exacerbating factors, and medical history is important for diagnosis[1]. The disorder constitutes a long-term maladaptation to a neuro-otological, medical, or psychological event that triggers vestibular symptoms and is usefully considered within the spectrum of other functional neurological disorders. Studies of PPV and CSD suggest that the long-term benefit of therapy likely depends on early initiation of treatment[2]. Years of chronicity usually suggest a higher degree of maladaptation, more severe disability, and more engrained illness beliefs. Despite efforts to unify the diagnosis of functional (somatoform) dizziness, patients present with a variety of triggers, perpetuating factors, and comorbidities, thus requiring individualized treatment. To date, no potential therapies for PPPD have been evaluated in randomized controlled clinical trials or been approved as a cure for this condition. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)[3,4], vestibular rehabilitation (VR)[4,5], cognitive-behavioral therapy (CBT)[6-9] and electrical stimulation[10] have been investigated as potential treatments for PPPD.

The Japanese herbal medicine hangebyakujutsutemmato (HBT; Kracie Co., Tokyo, Japan) has been used to prevent Meniere's disease, dizziness, nausea, hypotension, headache, and stomach disorders by eliminating excess water from the body[11-14]; in traditional Chinese herbal medicine, fluid retention is

attributable to the presence of unbalanced and mal-distributed water in the body[13]. HBT is composed of 12 crude herbal extracts which improve digestion to assist in the removal of excess fluid[15]. Regarding its potential as a therapy for PPPD, HBT has been reported as a potential treatment for CSD [13,16,17]. In addition, some reports indicated that HBT was effective in preventing dizziness caused by opioids[18] or pregabalin[19]. Thus, HBT is a promising drug based on its demonstrated effects on dizziness.

Our aim was to examine the efficacy of HBT for PPPD. We hypothesized that HBT could be an efficacious treatment for PPPD. In addition, we hypothesized that autonomic function disturbances could contribute to HBT responsiveness in patients with PPPD.

MATERIALS AND METHODS

Participants

Data, including sex, age, symptoms, and diagnosis, which were obtained on the day of ENT consultation, between January 1, 2020 and December 31, 2020, were collected from hospital medical records and analyzed. Patient inclusion criteria were as follows: (1) Age 20 to 100 years; (2) A score of more than 27 points on the Niigata PPPD questionnaire (NPQ, a 12-item questionnaire that evaluates the three exacerbating factors for PPPD[20]) after treatment with combined general non-Kampo drugs for vertigo/dizziness for more than 3 mo; and (3) Visited our hospital more than three times between January 1 , 2020 and December 31, 2020. The exclusion criteria were as follows: (1) Treatment with a Kampo medicine other than HBT; (2) Asthma or significant uncontrolled cardiac, pulmonary, gastrointestinal, renal, hepatic, endocrine, musculoskeletal, or oncological disorder or comorbidity that would likely prevent completion of the study; and (3) Less than two visits to our hospital. The clinical diagnosis of balance disorders was based on the diagnostic criteria published by the Japan Society for Equilibrium Research[21,22] and the Barany Society[1].

Primary and secondary endpoint measures and outcomes

This was a retrospective chart review. Patients were administered HBT extract (7.5 g/day) (Kracie Co., Tokyo, Japan; HBT group) or not (non-HBT group) for 3 mo. HBT was administered orally, twice daily, before eating. The quality of the HBT was standardized based on the Good Manufacturing Practices defined by the Ministry of Health, Labour and Welfare of Japan, and the quality of KB-37 was evaluated by 3D-HPLC analysis performed elsewhere. All patients took medications (non-Kampo) other than HBT for the treatment of vertigo/dizziness. We did not limit the use of other medications. In addition, all patients underwent VR for vestibular compensation, *via* the vestibulo-ocular reflex, three times at home.

Assessments were performed at baseline and every month after the start of the study. All participants completed clinical questionnaire-based surveys regarding balance disorders at each visit to our hospital (at least three times). The clinical surveys administered included the NPQ[20], dizziness handicap inventory (DHI)[23,24], hospital anxiety and depression scale (HADS)[25,26], orthostatic dysregulation (OD) Questionnaire[27,28], Graybiel's Motion Sickness Score[29], and Pittsburgh sleep quality index (PSQI)[30,31]. All participants underwent equilibrium testing at the first visit to our hospital. The equilibrium tests included static stabilometry, with or without foam posturography, to assess steady-state postural control and to detect visual and somatosensory dependence in patients[32]; the foulage test (FT), a stepping test on a force platform, to assess dynamic postural control[33-36]; the cervical vestibular-evoked myogenic potential (cVEMP) test to assess the function of the saccule-inferior vestibular nerve system[37]; ocular VEMP (oVEMP) testing to assess the function of the utricle-superior vestibular nerve system[38]; caloric testing to assess the function of the lateral semicircular canal-utricle-superior vestibular nerve system[39]; head-up tilt (HUT) testing to assess OD, which is related to autonomic dysfunction[40]; and nystagmus testing to assess vestibular function.

The methodological details and criteria for the questionnaires and tests are described in Supplementary Table 1. During stabilometry, the patients stood on a strain-gauge force platform (GP-5000 stabilometer; Anima, Tokyo, Japan) for 60 s with their eyes open with and without the foam rubber, and with their eyes closed with and without the foam rubber[41]. The measurements were performed under background noise conditions (approximately 50 dB). Somatosensory weighting was assessed by six parameters: The velocity and area of movement of the center of pressure with eyes closed/foam rubber (velocity, VCF; area, ACF) to assess vestibular weighting, the Romberg ratio of velocity and area with foam rubber (velocity; area-ARF) to assess visual weighting, and foam ratios (ratios of a measured parameter with to without the foam rubber) of velocity and area with eyes closed (velocity-VFCF and area-AFCF)[41]. The FT is a quantified stepping test performed at a set tempo of 120 bpm while standing upright with the arms placed at the side of the body, in a closed foot position, with the toes continuously touching the plate, so that the participant can change only the height of the heels to rise in alternation[33,42-44]. The parameters of the FT include the FT value (area of the front-back width of the locus) with eyes open and closed and the dynamic Romberg ratio (FT value of close/open eyes)[33,42-44]. During the cVEMP test, the patient's neck was rotated to the left as far as possible (approximately 70-80 degrees). The stimulation used clicks with a 120 dB sound pressure level lasting

Table 1 Patients' demographic information (mean ± SD)

	Non-HBT (*n* = 14)	HBT (*n* = 24)	*P* value
Age (yr)	63.5 ± 15.9	58.2 ± 18.7	0.19[a]
Sex (Male:Female)	3:11	1:23	0.21[b]
Vestibular disease	Meniere's disease: 12; BPPV: 2	Meniere's disease: 23; BPPV: 1	0.23[b]

[a]Unpaired *t*-test.
[b]Fisher's exact test.
HBT: Hangebyakujutsutemmato; SD: Standard deviation; BPPV: Benign paroxysmal positional vertigo.

0.1 ms, with a stimulation frequency of 5 Hz and an analysis time of 50 ms. The electromyographic responses to 200 stimuli were averaged and recorded using an evoked potential recorder with a band-pass filter of 20–2000 Hz (Neuropack; Nihon Kohden, Tokyo, Japan). To assess cVEMP amplitude, the asymmetry ratio (AR) was used, which was defined as the difference between the large amplitude (AL) and small amplitude (AS) of peak 13 to peak n23 divided by the sum of both amplitudes presented as a percentage, that is, [(AL - AS)/(AL + AS)] × 100 (%). The normal range of AR was defined as less than 33%[45]. During the oVEMP test, the patient maintained an upward gaze at 30° with the electrodes on the face just inferior to each eye. Stimulation included 0.1 ms clicks and 500 Hz short tone bursts (Neuropack). To assess oVEMP amplitude, AR was performed in a manner similar to cVEMP. The normal AR range was defined as less than 33%[46]. During the caloric test, stimulation was provided through sequential irrigation of each ear with 5 mL of water for 10 s. The maximum slow-phase velocity was measured using videonystagmography recordings (ENG, Nagashima, Tokyo, Japan). Canal paresis % (CP%) was calculated as described previously[47]. The CP% normal range was defined as less than 20%[48]. The HUT test was performed according to the method established by the Japan Society of Neurovegetative Research in 2015[49]. Non-invasive oscillatory measurements of blood pressure (BP), pulse rate, coefficient of variation of the R-R interval (CVRR), parasympathetic nerve function [high-frequency component (HF)], and sympathetic nerve function [low-frequency component (LF)/HF] were performed three times using an automated sphygmomanometer (Meijin + Circlemates; Crosswell, Tokyo, Japan) at the following time points: (1) After 5 min in the supine position; (2) After 1 min of standing; and (3) After 10 min of standing. The cuff of the BP-recording device was attached to the left arm, which was supported at the heart level throughout the study. The testing was conducted during the daytime, in a quiet environment, at a constant room temperature of 22 °C–25 °C to exclude the effects of chronobiologic factors on the outcomes of the test. The participants maintained a regular meal schedule but were restricted from smoking and caffeine ingestion for 6 h before the examination. The intake of foods and medications with sympathomimetic activity was also prohibited before the study. The results were determined as positive or negative according to the outcome of the HUT test and the international scientific definition of OD (Supplementary Table 1)[40]. Regarding systolic BP, diastolic BP, heart rate, CVRR, HF, and LF/HF, the change ratio was calculated as a measured parameter of (2)/(1) for the immediate change ratio and (3)/(2) for the delayed change ratio. Nystagmus was evaluated using an infrared charge-coupled device camera. When pathologic nystagmus (*i.e.*, spontaneous nystagmus or positional nystagmus) was observed, the test result was considered positive.

The primary outcome was the therapeutic effect on PPPD and the secondary outcome was autonomic dysfunction for the prediction of benefit.

Statistical analyses

Power and sample size calculations were conducted before and after data collection using PS software (Ver. 3.1.6, Vanderbilt University, Nashville, TN)[50]. The statistical review of the study was performed by a biomedical statistician. For non-parametric analysis of subjective variables which were not normally distributed, the Wilcoxon signed-rank test was used to investigate changes in the questionnaire scores. For parametric analysis of subjective variables which were normally distributed, unpaired *t*-tests were used to investigate age variables. Fisher's exact test was used to compare sex and vestibular disease variables with a non-normal distribution. Regarding the primary outcome, changes in NPQ scores were compared using a one-way analysis of variance and post-hoc Tukey test, and NPQ scores between groups were compared using the Kruskal–Wallis test and the post-hoc two-stage linear step-up procedure; this was done to avoid an inflated Type I error rate because the data were normally distributed. NPQ score improvements were compared using a mixed-effect analysis and post-hoc Bonferroni's multiple comparison test because of the number of missing values. Residual plots were used to confirm the correctness of the assumptions made for both primary outcomes. Regarding secondary outcomes, multivariate regression analysis was performed to identify HBT responders. Questionnaire survey data and equilibrium test results at the first visit to our hospital were used for the HBT group. The outcome variable was the rate of improvement in total NPQ scores after 2 mo of HBT treatment. Due to the small number of participants, multivariate regression analysis was performed to

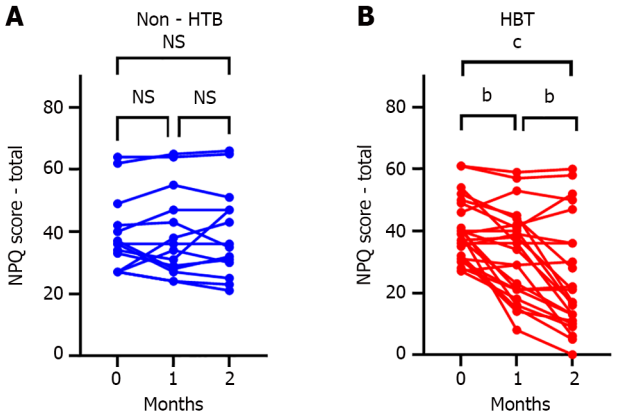

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Figure 1 Niigata persistent postural-perceptual dizziness questionnaire score changes after hangebyakujutsutemmato treatment for persistent postural-perceptual dizziness. A: No statistically significant changes in Niigata persistent postural-perceptual dizziness questionnaire (NPQ) scores were seen in the non-hangebyakujutsutemmato (HBT) group (baseline *vs* 1 mo, $P = 0.98$; 1 mo *vs* 2 mo, $P = 0.94$; baseline *vs* 2 mo, $P = 0.92$); B: In the HBT group, NPQ scores showed a statistically significant decrease (baseline *vs* 1 mo, $P = 0.002$; 1 mo *vs* 2 mo, $P = 0.003$; baseline *vs* 2 mo, $P < 0.001$). $^{b}P < 0.01$; $^{c}P < 0.001$. NS: Not significant; NPQ: Niigata PPPD questionnaire; HBT: Hangebyakujutsutemmato; PPPD: Persistent postural-perceptual dizziness.

divide the explanatory variables into equilibrium tests, HUT results, and questionnaire survey results. The model was created after confirming the variance inflation factor. The explanatory variances were selected according to the Akaike information criterion. Missing values were imputed using the RF method. There were no outliers in the analysis of either primary or secondary outcomes. Statistical significance was set at $P < 0.05$. Evaluations were determined as 'not applicable' if the calculated sample size after data collection was insufficient for statistical analysis. All statistical analyses were performed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California United States, www.graphpad.com).

RESULTS

Patient information

Thirty-eight outpatients were included in this study. A total of 14 patients (three men, 11 women; mean ± SD, 63.5 ± 15.9 years) received treatment without HBT (non-HBT group) and 24 patients (one man, 23 women; mean age, 58.2 ± 18.7 years) received combination treatment with HBT (HBT group). Table 1 shows the clinical characteristics of the participants in the non-HBT and HBT groups. Characteristics such as sex, age, and vestibular disease were not significantly different between the two groups (Table 1, age, $P = 0.19$; sex, $P = 0.21$; vestibular disease, $P = 0.23$).

NPQ scores improved in the HBT group

No statistically significant changes in NPQ scores were observed in the non-HBT group (Figure 1A: Baseline *vs* 1 mo, $P = 0.98$; 1 mo *vs* 2 mo, $P = 0.94$; baseline *vs* 2 mo, $P = 0.92$). In the HBT group, NPQ scores showed a statistically significant decrease (Figure 1B: Baseline *vs* 1 mo, $P = 0.002$; 1 mo *vs* 2 mo, $P = 0.003$; baseline *vs* 2 mo, $P < 0.001$). In the non-HBT group, there was no significant difference in the NPQ subcategory scores for upright posture/walking (Figure 2A: Baseline *vs* 1 mo, $P = 0.67$; 1 mo *vs* 2 mo, $P = 0.73$; baseline *vs* 2 mo, $P = 0.41$) or movement (Figure 2B: Baseline *vs* 1 mo, $P = 0.50$; 1 mo *vs* 2 mo, $P > 0.99$; baseline *vs* 2 mo, $P = 0.38$), while the score for visual stimulation showed a significant difference at month 2 (Figure 2C: Baseline *vs* 1 mo, $P = 0.11$; 1 mo *vs* 2 mo, $P = 0.53$; baseline *vs* 2 mo, $P = 0.02$). In the HBT group, NPQ subcategory scores showed statistically significant differences for upright posture/walking (Figure 2D: Baseline *vs* 1 mo, $P = 0.04$; 1 mo *vs* 2 mo, $P = 0.005$; baseline *vs* 2 mo, $P < 0.001$), movement (Figure 2E: baseline *vs* 1 mo, $P = 0.01$; 1 mo *vs* 2 mo, $P = 0.006$; baseline *vs* 2 mo, $P < 0.001$), and visual stimulation (Figure 2F: Baseline *vs* 1 mo, $P = 0.002$; 1 mo *vs* 2 mo, $P = 0.03$; baseline *vs* 2 mo, $P < 0.001$). Comparisons between groups revealed significant differences in the rate of NPQ improvement (Figure 3A: 1 mo, $P = 0.16$; 2 mo, $P = 0.009$). There were significant differences in the NPQ total score (Figure 3B: Baseline, $P > 0.99$; 1 mo, $P = 0.89$; 2 mo, $P = 0.02$), upright posture/walking score (Figure 3C: Baseline, $P > 0.99$; 1 mo, $P = 0.21$; 2 mo, $P = 0.005$), and movement score (Figure 3D: Baseline, $P > 0.99$, 1 mo, $P = 0.87$; 2 mo, $P = 0.03$) at 2 mo between the two groups, while the visual stimulation score showed no significant differences (Figure 3E: Baseline, $P = 0.11$; 1 mo, $P > 0.99$; 2 mo, $P = 0.06$).

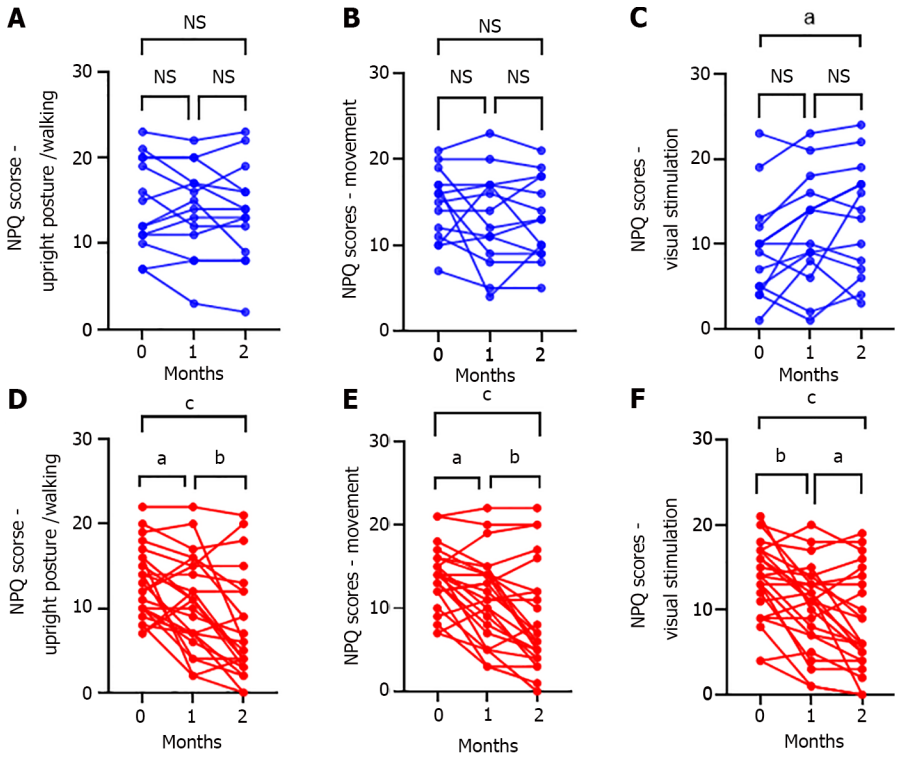

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Figure 2 Niigata persistent postural-perceptual dizziness questionnaire subcategory score changes after hangebyakujutsutemmato treatment for persistent postural-perceptual dizziness. A-C: There was no significant difference in the Niigata persistent postural-perceptual dizziness questionnaire (NPQ) subcategory scores in the non-hangebyakujutsutemmato (HBT) group except for the NPQ visual subcategory; A: Upright posture/walking: Baseline *vs* 1 mo, $P = 0.67$; 1 mo *vs* 2 mo, $P = 0.73$; baseline *vs* 2 mo, $P = 0.41$; B: Movement: Baseline *vs* 1 mo, $P = 0.50$; 1 mo *vs* 2 mo, $P > 0.99$; baseline *vs* 2 mo, $P = 0.38$; C: Visual stimulation: Baseline *vs* 1 mo, $P = 0.11$; 1 mo *vs* 2 mo, $P = 0.53$; baseline *vs* 2 mo, $P = 0.02$); D-F: In the HBT group, NPQ subcategory scores showed statistically significant differences; D: Upright posture/walking: Baseline *vs* 1 mo, $P = 0.04$; 1 mo *vs* 2 mo, $P = 0.005$; baseline *vs* 2 mo, $P < 0.001$; E: Movement: Baseline *vs* 1 mo, $P = 0.01$; 1 mo *vs* 2 mo, $P = 0.006$; baseline *vs* 2 mo, $P < 0.001$; F: Visual stimulation, baseline *vs* 1 mo, $P = 0.002$; 1 mo *vs* 2 mo, $P = 0.03$; baseline *vs* 2 mo, $P < 0.001$. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$. NS: Not significant; NPQ: Niigata PPPD questionnaire; HBT: Hangebyakujutsutemmato; PPPD: Persistent postural-perceptual dizziness.

Other factors were not influenced by HBT treatment in PPPD patients

To examine the effect of HBT on other factors, we compared the questionnaire survey results at baseline, 1 mo, and 2 mo. No statistically significant differences in the DHI, including subcategories; HADS, including subcategories; OD scores; Graybiel's motion sickness scores; or PSQI at baseline, were observed between the two groups (Table 2).

HBT responders had autonomic dysfunction, unstable balance, CP, anxiety, and poor sleep quality at baseline

To identify HBT responders among PPPD patients, we performed multivariate regression analysis. We identified the rate of improvement in NPQ scores. ACF, ARF, VFCF, AFCF in static stabilometry, CP% of the caloric test, and the existence of OD at the first visit to our hospital were significant factors for HBT responsiveness (Table 3: ACF, $P = 0.02$; ARF, $P = 0.01$; VFCF, $P = 0.03$; AFCF, $P = 0.03$; CP%, $P = 0.03$; OD, $P < 0.001$). To investigate the precise influence of OD on HBT responders, we performed multivariate regression analysis using the explanatory variables of the HUT test. The results showed that the immediate change ratio of HR and CVRR and delayed change ratio of HF and LF/HF were significant factors for HBT responsiveness in PPPD patients (Table 4: Immediate change ratio of HR, $P = 0.009$; immediate change ratio of CVRR, $P = 0.03$; delayed change ratio of HF, $P = 0.006$; delayed change ratio of LF/HF, $P = 0.04$). In addition, regarding the questionnaire surveys, dizziness handicap index–emotional (DHI-E), HADS-anxiety (HADS-A), and PSQI were significant factors for HBT responsiveness (Table 5: DHI-E, $P = 0.01$; HADS-A, $P = 0.003$; PSQI, $P = 0.01$).

DISCUSSION

PPPD is a newly defined diagnostic syndrome that unifies the key features of PPV, CSD, and related disorders[1]. Although the exact pathophysiology of PPPD remains to be elucidated, data from

Table 2 Other factors influenced by hangebyakujutsutemmato treatment in Persistent postural-perceptual dizziness patients

			Non-HBT (*n* = 14)	HBT (*n* = 24)	*P* value[1]
DHI		Baseline	49.6 ± 24.6	50.8 ± 20.1	0.44
		1 mo	45.7 ± 25.8	43.0 ± 3.0	0.37
		2 mo	42.7 ± 25.0	38.8 ± 24.3	0.32
Subcategory	DHI-P	Baseline	11.9 ± 7.6	14.9 ± 6.2	0.11
		1 mo	11.4 ± 7.1	11.8 ± 7.1	0.43
		2 mo	11.0 ± 6.8	11.3 ± 6.9	0.46
	DHI-E	Baseline	19.6 ± 8.9	16.7 ± 8.6	0.17
		1 mo	17.3 ± 9.7	14.7 ± 9.0	0.21
		2 mo	15.3 ± 9.5	12.7 ± 9.7	0.21
	DHI-F	Baseline	18.1 ± 11.3	19.3 ± 8.8	0.38
		1 mo	17.0 ± 11.8	16.5 ± 10.1	0.45
		2 mo	16.4 ± 10.6	14.8 ± 9.7	0.32
HADS		Baseline	15.8 ± 8.3	15.0 ± 7.3	0.39
		1 mo	15.6 ± 7.8	13.8 ± 8.6	0.25
		2 mo	15.6 ± 8.6	13.0 ± 9.5	0.19
Subcategory	HADS-A	Baseline	8.9 ± 5.0	9.0 ± 4.0	0.49
		1 mo	8.1 ± 4.4	7.8 ± 4.4	0.42
		2 mo	7.9 ± 5.0	7.7 ± 4.8	0.45
	HADS-D	Baseline	6.9 ± 4.1	6.1 ± 4.3	0.29
		1 mo	7.6 ± 4.5	6.0 ± 4.7	0.16
		2 mo	7.7 ± 4.8	5.3 ± 5.3	0.08
OD score		Baseline	6.1 ± 2.2	7.8 ± 5.4	0.08
		1 mo	5.9 ± 2.6	5.9 ± 2.9	0.48
		2 mo	5.6 ± 3.0	5.6 ± 2.6	0.48
Graybiel's motion sickness score		Baseline	26.0 ± 11.0	25.8 ± 11.2	0.47
		1 mo	19.3 ± 7.6	19.9 ± 8.4	0.41
		2 mo	23.3 ± 12.4	18.1 ± 6.9	0.08
PSQI		Baseline	8.9 ± 3.5	10.0 ± 3.4	0.19
		1 mo	8.6 ± 3.0	9.0 ± 4.6	0.37
		2 mo	8.5 ± 3.1	9.6 ± 4.1	0.19

[1]Wilcoxon signed-rank test.

To examine the effects of HBT on other factors, we compared the questionnaire survey at baseline, 1 mo, and 2 mo. No statistically significant differences in the DHI including subcategories, HADS including subcategories, OD scores, Graybiel's motion sickness scores, or PSQI at baseline were observed between the two groups. HBT: Hangebyakujutsutemmato; DHI: Dizziness handicap inventory; HADS: Hospital anxiety and depression scale; HADS-A: Hospital anxiety and depression scale-anxiety; HADS-D: Hospital anxiety and depression scale–depression subscale; OD: Orthostatic dysregulation; PSQI: Pittsburg sleep quality index.

physiological investigations and rapidly emerging advanced structural and functional neuroimaging studies of patients with PPV, CSD, and PPPD have revealed three key mechanisms by which this disorder is thought to develop: Stiffened posture, a shift in processing spatial orientation information to favor visual over vestibular inputs, and failure of higher cortical mechanisms to modulate the first two processes[51,52]. Maladaptive cognitive-behavioral responses commonly add secondary psychological and functional morbidity, such as fear of falling, anxiety or depressive disorders, and functional gait abnormalities[53,54].

Table 3 Equilibrium test factors related to Niigata persistent postural-perceptual dizziness questionnaire improvement at 2 mo

		Estimate	SE	*t* value	*P* value
	(Intercept)	-0.18	0.31	-0.58	0.571
Static stabilometry	ACF	-0.01	0.005	-2.53	0.02[a]
	VRF	-0.30	0.19	-1.55	0.14
	ARF	0.33	0.11	2.99	0.01[a]
	VFCF	0.33	0.14	2.29	0.03[a]
	AFCF	-0.09	0.04	-2.34	0.03[a]
Dynamic stabilometry	FT value in closed eye	-0.03	0.02	-1.29	0.21
Vestibular function	CP (%) of caloric test	0.004	0.002	2.28	0.03[a]
	AR (%) of cVEMP	0.005	0.003	1.46	0.16
	AR (%) of oVEMP	-0.008	0.005	-1.47	0.16
Autonomic function	OD	0.77	0.11	6.65	< 0.001[b]

[a]$P < 0.05$.
[b]$P < 0.01$.
VCF: Center of pressure velocity in the eyes closed/foam rubber condition; ACF: Envelopment area tracing by movement of the center of pressure in the eyes closed/foam rubber condition; VRF: Romberg's ratio of velocity with foam rubber; ARF: Romberg's ratio of area with foam rubber; VFCF: Foam ratio of velocity in the eyes closed/foam rubber condition; FCF: Foam ratio of area in the eyes closed/foam rubber condition; FT value: Foulage test value; CP (%): Canal paresis in caloric test; AR (%): Asymmetry ratio; cVEMP: Cervical vestibular evoked myogenic responses; oVEMP: Ocular vestibular-evoked myogenic responses; OD: Orthostatic dysregulation. Residual standard error = 0.20 (df = 13; multiple R-squared = 0.81; adjusted R-squared = 0.67, F-statistic = 5.77 (df, 10 and 13; *P* value = 0.002, Akaike information criterion = -68.7).

Therefore, strategies for the treatment of PPPD are as follows: strategy 1, therapy for comorbidities including vestibular diseases; strategy 2, sensory reweighting of posture; and strategy 3, increased tolerance of a perceived stimulus *via* desensitizing. SSRIs and SNRIs act on serotoninergic pathways in the CNS[3,55] and thus address strategies 1 and 2. Since rehabilitation from PPPD relies on "re-adaptation" of the vestibular and balance systems, vestibular suppressant drugs such as antihistamines and benzodiazepines can be expected to delay rather than hasten rehabilitation and should be avoided if possible[56]. VR is an umbrella term for a range of physical treatments that aim to compensate or restore impaired balance in various vestibular and neurological disorders. For example, PPPD patients often exhibit hyper-visual sensation, which VR aims to desensitize using habituation exercises and relaxation techniques[5,6]. As such, VR may address strategies 2 and 3. CBT was responsible for guiding self-observation on physical, emotional, and psychosocial levels to break out of maladaptive cognitive-behavioral cycles. Desensitizing exercises can be used to increase the tolerance of perceived disequilibrium and reduce automatic "high-risk" postural strategies[7,8]. Thus, CBT may address strategy 3. The present results showed that NPQ scores improved significantly in patients treated with HBT compared with those not treated with HBT. Notably, the visual score in the HBT group showed significantly greater improvement compared with the non-HBT group.

HBT is a powdered extract obtained by spray drying a hot water extract mixture of the following 12 crude herbal drug extracts: Citrus unshiu peel (1.0 g, 12%), Pinellia tuber (1.0 g, 12%), Atractylodes rhizome (1.0 g, 12%), Atractylodes Lancea Rhizome (1.0 g, 12%), Poria sclerotium (1.0 g, 12%), gastrodia tuber (0.75 g, 8%), malt (0.75 g, 8%), Astragalus root (0.5 g, 6%), Alisma Tuber (0.5 g, 6%), ginseng (0.5 g, 6%), Phellodendron bark (0.325 g, 4%), and ginger (0.1625 g, 2%). Supplementary Figure 1 shows the components and effects of HBT. HBT was shown to alleviate inner ear immune injury in a rat model[19] and disturbance of equilibrium resulting from pregabalin in a rat model of neuropathic pain[19]. The components of HBT have various pharmacological effects on vertigo/dizziness/vomit/nausea. Alkaloids in Pinellia Tuber, Atractylenolide III in Atractylodes rhizome, and 6-shogaol in ginger affect gastroesophageal vagal nodose C-fibers to relieve nausea/vomiting and gastrointestinal discomfort[57-59] when vertigo/dizziness occurs. Atractylenolide III in Atractylodes rhizome, triterpenes, and polysaccharides in Poria sclerotium, and triterpenoids in Alisma Tuber have antidiuretic effects[13,15,60,61], which can alleviate endolymphatic hydrops in the inner ear. Berberine in Phellodendron bark has effects on cyclooxygenase-2, which plays a key role in prostaglandin synthesis, resulting in anti-inflammatory activity[62], while vanillin in Gastrodia Tuber has been shown to protect hippocampal CA1 neurons against ischemic cell death and to produce a significant increase in neuronal survival and antioxidant activity against lipid peroxidation[63], which can protect against brain neuronal injury *via* inner ear damage. Moreover, vanillin in Gastrodia Tuber, ginsenosides in ginseng, and atractylenolide III in Atractylodes Rhizome have antidepressant effects[59,64,65], which can prevent worsening of

Table 4 Head-up tilt test factors related to Niigata persistent postural-perceptual dizziness questionnaire improvement at 2 mo

	Variable	Estimate	SE	*t* value	*P* value
	(Intercept)	-16.8	4.78	-3.51	0.004[b]
	Age	0.01	0.006	2.04	0.06
	Sex	-0.78	0.60	-1.31	0.21
INOH	Immediate change ratio (sBP)	2.41	1.42	1.69	0.11
	Immediate change ratio (dBP)	2.82	1.72	1.63	0.13
Delayed OH	Delayed change ratio (sBP)	1.36	0.94	1.44	0.17
	Delayed change ratio (dBP)	1.67	1.04	1.60	0.13
PoTS	Immediate change ratio (HR)	4.39	1.40	3.13	0.009[b]
Parasympathetic nervous system	Immediate change ratio (CVRR)	0.88	0.37	2.36	0.03[a]
	Delayed change ratio (HF)	2.27	0.68	3.34	0.006[b]
Sympathetic nervous system	Immediate change ratio (L/H)	0.09	0.07	1.21	0.24
	Delayed change ratio (L/H)	0.59	0.26	2.26	0.04[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
Residual standard error = 0.29 (df = 11); multiple R-squared = 0.66; adjusted R-squared = 0.32; F-statistic = 1.95 (df, 11 and 11); *P* value = 0.14; Akaike information criterion = -49.7. HF: High-frequency component; L/H: Low-frequency component/high-frequency component; CVRR: Coefficient of variation of the R-R interval; INOH: Instantaneous orthostatic hypotension; OH: Orthostatic hypotension; PoTS: Postural tachycardia syndrome; NPQ: Niigata PPPD questionnaire; HBT: Hangebyakujutsutemmato; PPPD: Persistent postural-perceptual dizziness.

Table 5 Questionnaire survey factors related to Niigata persistent postural-perceptual dizziness questionnaire improvement at 2 mo

Variables	Estimate	SE	*t* value	*P* value
(Intercept)	1.28	0.22	5.59	0.00002[c]
DHI-E	0.03	0.01	2.56	0.01[a]
DHI-F	-0.02	0.01	-1.86	0.07
HADS-A	-0.05	0.01	-3.30	0.003[b]
PSQI	-0.05	0.01	-2.80	0.01[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Residual standard error = 0.27 (df = 19); multiple R-squared = 0.51; adjusted R-squared = 0.41; F-statistic = 5.02 (df, 4 and 19); *P* value = 0.006; Akaike information criterion = -57.4. DHI-E: Dizziness handicap index–emotional; DHI-F: Dizziness handicap index–functional; HADS-A: Hospital anxiety and depression scale-anxiety; PSQI: Pittsburg sleep quality index.

PPPD symptoms[1]. Hesperidin in Citrus unshiu peel, atractylenolide III in Atractylodes rhizome, and ginsenosides in ginseng activate cyclic AMP response element binding protein (CREB)/the brain-derived neurotrophic factor (BDNF) pathway in the hippocampus[59,64,65], similar to the pharmacological actions of SSRIs/SSNIs on serotonergic neurotransmission (5-HT-CRF pathway)[66,67], which increases ghrelin signaling and activates the BDNF/trkB/CREB pathway in the cerebral cortex and vestibular nucleus[68]. Thus, in PPPD patients, HBT is hypothesized to have an anti-diuretic effect in the inner ear, consistent with strategy 1, while CREB-BDNF activation in the hippocampus, cerebral cortex, and vestibular nucleus has the same action as SSRIs/SSNIs, which has therapeutic effects in PPPD[55,69], and is consistent with strategies 2 and 3. In addition, gastroesophageal vagal nerve activation by HBT[58,70] might produce feedback resulting in somatosensory suppression *via* the autonomic nervous system in the hypothalamus, anterior cingulate gyrus, and insular cortex[71,72], resulting in sensory reweighting to establish a balance between the systems and increased tolerance to the perceived

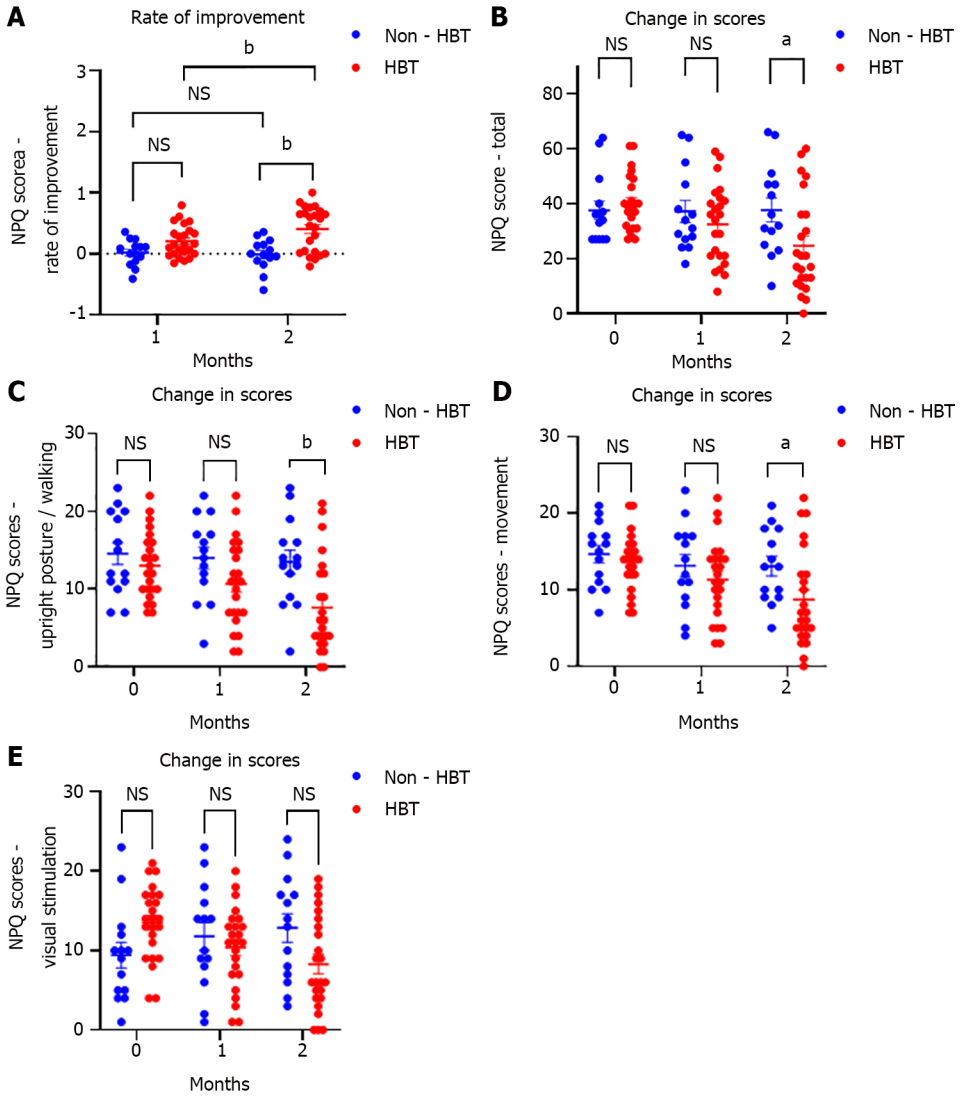

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Figure 3 Comparison of rate of improvement and Niigata persistent postural-perceptual dizziness questionnaire scores between groups. A: Comparisons between groups revealed significant differences in the rate of Niigata persistent postural-perceptual dizziness questionnaire (NPQ) improvement (1 mo, $P = 0.16$; 2 mo, $P = 0.009$); B-E: There were significant differences in NPQ total scores, upright posture/walking scores, and movement scores at 2 mo between groups; B: Total score: Baseline, $P > 0.99$; 1 mo, $P = 0.89$; 2 mo, $P = 0.02$; C: Upright posture/walking: Baseline, $P > 0.99$; 1 mo, $P = 0.21$; 2 mo, $P = 0.005$; D: Movement: Baseline, $P > 0.99$; 1 mo, $P = 0.87$; 2 mo, $P = 0.03$; E: Visual stimulation: Baseline, $P = 0.11$; 1 mo, $P > 0.99$; 2 mo, $P = 0.06$. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$. Data represent mean and standard error (vertical bars). NPQ: Niigata PPPD questionnaire; HBT: Hangebyakujutsutemmato; PPPD: Persistent postural-perceptual dizziness; NS: Not significant.

stimulus (*i.e.*, strategies 2 and 3).

We performed multiple regression analysis to identify patients with PPPD who responded to HBT. Our results showed that PPPD with autonomic dysfunction; body balance dysfunction related to vestibular (ACF), visual (ARF), or somatosensory (VFCF and AFCF) factors[41]; unilateral CP, anxiety, and poor sleep quality at baseline were characteristics of HBT responders. In particular, changes in HR and CVRR with upright posture and delayed changes in HF and LF/HF during standing, which are deeply related to autonomic function, were important factors for HBT responses in PPPD patients. These results suggest that the effect of HBT in patients with PPPD might be to improve antecedent vestibular disease and autonomic dysfunction modified by mood disorders. Therefore, our hypothesis regarding the mechanism of action of HBT in PPPD (strategies 1-3) might be correct.

Limitations

There are several limitations to this study. First, since HBT contains a variety of herbal ingredients, it is difficult to ascertain which ingredients affected PPPD. Second, patients were not treated solely with HBT, but also with non-Kampo drugs for vertigo/dizziness and VR. Third, the patient population in this study was small. Randomized blinded trials with a non-HBT treatment group are needed to provide more robust evidence. Fourth, only subjective investigator-rated and/or patient-self-reported

outcome measures were used as study endpoints, potentially introducing various biases. Markers for the prognosis of PPPD are necessary.

CONCLUSION

The present study is the first to demonstrate that HBT is an effective adjunct treatment for PPPD. It was hypothesized that several herbal ingredients in HBT could improve diuretic conditions in the inner ear, the functionality of the CREB-BDNF pathway in the brain, and digestive dysfunction, resulting in sensory reweighting to establish balance of the systems involved in PPPD. PPPD patients who are HBT responders might have antecedent vestibular disease and modified autonomic dysfunction as a result of mood disorders.

ARTICLE HIGHLIGHTS

Research background

Persistent postural-perceptual dizziness (PPPD) is characterized by a shift in processing spatial orientation information to favor visual or somatosensory information over vestibular inputs as well as failure of higher cortical mechanisms.

Research motivation

To date, no potential therapies for PPPD have been evaluated in randomized controlled clinical trials or been approved as a cure for this condition. Hangebyakujututemmato (HBT) has been reported as a potential treatment for PPPD.

Research objectives

Our aim was to examine the efficacy of HBT in PPPD.

Research methods

Patients were administered HBT extract (7.5 g/day), or not, for 3 mo. Assessments such as equilibrium tests were performed at baseline and every month after the start of the study. Multivariate regression analysis was performed to identify HBT responders.

Research results

The Kampo medicine, HBT, was effective as an adjunctive therapy for PPPD. In addition, HBT responders had autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality at baseline.

Research conclusions

HBT may be an effective adjunct treatment for PPPD. We identified the characteristics of the HBT responders.

Research perspectives

According to our results, and previous reports, several herbal ingredients in HBT might improve autonomic function and the cyclic AMP response element binding protein/the brain-derived neurotrophic factor pathway, resulting in sensory reweighting to establish a balance between the systems involved in PPPD.

FOOTNOTES

Author contributions: Miwa T contributed to the investigation, project administration, methodology, software, resources, visualization, writing–original draft, data curation, formal analysis, supervision, conceptualization, validation, writing–review and editing; Kanemaru SI contributed to the methodology, supervision, conceptualization; All authors approved the final version of the manuscript.

Institutional review board statement: The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Kitano Hospital (protocol code 2104002 for the approval).

Informed consent statement: Written informed consent was obtained from all participants prior to study inclusion.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The data are available upon reasonable request from the corresponding author.

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Country/Territory of origin: Japan

ORCID number: Toru Miwa 0000-0002-5977-0056; Shin-ichi Kanemaru 0000-0001-8424-9345.

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