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Retrospective Cohort Study

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

Hangebyakujututemmato for PPPD treatment

Toru Miwa, Shin-ichi Kanemaru

Abstract

BACKGROUND

Persistent postural-perceptual dizziness is a functional disorder, typically preceded by acute vestibular disorders. Persistent postural-perceptual dizziness 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 potential therapies for persistent postural-perceptual dizziness have been approved. Kampo medicine Hangebyakujutsutemmato has been reported to alleviate disturbances of equilibrium. We hypothesize that Hangebyakujutsutemmato is beneficial as a therapy for persistent postural-perceptual dizziness.

AIM

The study aimed to examine the feasibility of Hangebyakujutsutemmato for the treatment of persistent postural-perceptual dizziness.

METHODS

Patients with persistent postural-perceptual dizziness were enrolled in the study and divided into two groups: the Hangebyakujutsutemmato group (n = 24) and the non-Hangebyakujutsutemmato group (n = 14). The study participants completed questionnaire surveys (Niigata PPPD Questionnaire [NPQ], Dizziness Handicap Inventory [DHI], Hospital Anxiety and Depression Scale [HADS], Orthostatic Dysregulation [OD] Questionnaire, Pittsburg Sleep Quality Index [PSQI], and motion sickness scores) before and after Hangebyakujutsutemmato treatment. Additionally, to identify Hangebyakujutsutemmato responders, multivariate regression analysis using the results of the questionnaire surveys and equilibrium tests, including the stabilometry, caloric test, vestibular evoked myogenic response test, and head-up tilt test, was performed.

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 Hangebyakujutsutemmato, and 24 patients (1 man, 23 women; mean age, 58.2 ± 18.7 years) received combination treatment with Hangebyakujutsutemmato. Following Hangebyakujutsutemmato treatment, NPQ scores were significantly decreased in the Hangebyakujutsutemmato group (baseline 40.1 ± 10.0 vs. 2 mo 24.6 ± 17.7, P < 0.001). No statistically significant changes in NPQ scores were observed in the non-Hangebyakujutsutemmato group (baseline 38.6 ± 12.2 vs. 2 mo 39.4 ± 14.4, *P* = 0.92). Multivariable regression analysis revealed that stabilometry (*P* = 0.02), the caloric test (*P* = 0.03), head-up tilt test (P < 0.001), HADS (*P* = 0.003), and PSQI (*P* = 0.01) were factors associated with Hangebyakujutsutemmato responsiveness among persistent postural-perceptual dizziness patients.

CONCLUSION

Hangebyakujutsutemmato may be an effective adjunct in persistent postural-perceptual dizziness treatment. High responders to Hangebyakujutsutemmato may have autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality.

Key Words: Hangebyakujutsutemmato; Kampo medicine; PPPD; NPQ score; sensory reweighting; Treatment responder

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Core Tip: 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. In addition, HBT responders had autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality. According to our results and previous reports, it was predicted that several herbal ingredients in HBT might improve autonomic function and the CREB-BDNF pathway, resulting in sensory reweighting to establish a balance between the systems involved in PPPD.

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 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 and are exacerbated by an upright posture/walking, active or passive movement, and exposure to moving 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 PPPD 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 the 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 have been approved as a cure for this condition. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors

(SNRIs)[3,4], vestibular rehabilitation (VR)[4-6], cognitive-behavioral therapy (CBT)[7-9], 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[11-15]; in traditional Chinese herbal medicine, fluid retention is attributable to the presence of unbalanced and mal-distributed water in the body[16]. HBT is composed of 12 crude herbal extracts which improve digestion to assist in the removal of excess fluid[17,18]. Regarding its potential as a therapy for PPPD, HBT has been reported as a potential treatment for CSD[11,12,15]. In addition, some reports indicate that HBT is effective in preventing dizziness caused by opioids[19] or pregabalin[20]. Thus, HBT is a promising drug based on its demonstrated effects on dizziness.

Our aim is to examine the feasibility of HBT for PPPD. Therefore, we hypothesized that HBT could be a feasible therapy for PPPD. In addition, we hypothesized that autonomic function 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 and December 31, 2020, were collected from hospital medical records and analyzed. Patient inclusion criteria were as follows: (i) age 20 to 100 years; (ii) 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[21]) after treatment with combined general non-Kampo drugs for vertigo/dizziness for more than 3 mo; and (iii) visited our hospital more than three times between January 1 and December 31, 2020. The exclusion criteria were as follows: (i) treatment with a Kampo medicine other than HBT; (ii) 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 (iii) patients who did not visit our hospital more than twice. The clinical diagnosis of balance disorders was based on the diagnostic criteria published by the Japan Society for Equilibrium Research[22,23] 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 vestibular rehabilitation to acquire 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(21), Dizziness Handicap Inventory (DHI)[24,25], Hospital Anxiety and Depression Scale (HADS)[26,27], Orthostatic Dysregulation (OD) Questionnaire[28,29], Graybiel's Motion Sickness Score[30], and Pittsburgh Sleep Quality Index (PSQI)[31,32]. All participants underwent equilibrium testing at the initial 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[33]; the foulage test, a stepping test on a force platform, to assess dynamic postural control[34-36]; 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 based on six parameters: the velocity and area of movement of the center of pressure (COP) with eyes closed/foam rubber (velocity, VCF; area, ACF) to assess vestibular weighting, the Romberg ratio of velocity and area with foam rubber (velocity; VRF, 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 foulage test 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, a closed foot position, and the toes continuously touching the plate constantly, so that the subject can change only the height of the heels to rise in alternation[34-36,42]. The parameters of the foulage test 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)[34,35,42]. During the cVEMP test, the patient's neck was rotated to the left side as far as possible (approximately 70-80 degrees). The stimulation utilized clicks with a 120 dB sound pressure level lasting 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)]x100(%).

The normal range of AR was defined as less than 33%[43]. 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%[44]. 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 (MVS) was measured using videonystagmography recordings (ENG, Nagashima, Tokyo, Japan). Canal paresis % (CP%) was calculated as described previously[45]. The CP% normal range was defined as less than 20%[46]. The HUT test was performed according to the method established by the Japan Society of Neurovegetative Research in 2015[47]. Non-invasive oscillatory measurements of blood pressure (BP), pulse rate, CVRR, parasympathetic nerve function (HF), and sympathetic nerve function (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 22–25°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 hours 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)[48]. 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 (ANOVA) 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 of Benjamini *et al*; 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 subjects, multivariate regression analysis was performed to divide the explanatory variables into equilibrium tests, HUT results, and questionnaire survey results. The model was created after confirming the variance inflation factor (VIF). The explanatory variances

were selected according to the Akaike information criterion (AIC). 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 USA, www.graphpad.com).

RESULTS

Patient information

Thirty-eight outpatients were included in this study. A total of 14 patients (three men, 11 women; mean age ± standard deviation, 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 diseases 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 (Fig 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 (Fig 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 (Fig 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 (Fig 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 (Fig 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 (Fig 2d: baseline vs. 1 mo, P = 0.04; 1 mo vs. 2 mo, P = 0.005; baseline vs. 2 mo, P < 0.001), movement (Fig 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 (Fig 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 (Fig 3a: 1 mo, P = 0.16; 2 mo, P = 0.009). There were significant differences in the NPQ total score (Fig 3b: baseline, P > 0.99; 1 mo, P = 0.89; 2 mo, P = 0.02), upright posture/walking score (Fig 3c: baseline, P > 0.99; 1 mo, P = 0.21; 2 mo, P = 0.005), and movement score (Fig 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 (Fig 3e: baseline, P = 0.11; 1 mo, P > 0.99; 2 mo, P = 0.06).

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, canal paresis, 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 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 L/H 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 L/H, $P = 0.04$). In addition, regarding the questionnaire surveys, DHI-E, 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 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[3,49-54]. Maladaptive cognitive-behavioral responses commonly add secondary psychological and functional morbidity, such as fear of falling, anxiety or depressive disorders, and functional gait abnormalities. 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[3,4] 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[55]. 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[4-6]. 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[7-9]. Thus, CBT may address Strategy 3.

The present results showed that NPQ scores were significantly improved 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 (1.0g, 12%), Pinellia tuber (1.0g, 12%), Atractylodes rhizome (1.0g, 12%), Atractylodes Lancea Rhizome (1.0g, 12%), Poria sclerotium (1.0g, 12%), gastrodia tuber (0.75g, 8%), malt (0.75g, 8%), Astragalus root (0.5g, 6%), Alisma Tuber (0.5g, 6%), ginseng (0.5g, 6%), Phellodendron bark (0.325g, 4%), and ginger (0.1625g, 2%). Supplementary Figure 2 shows the components and effects of HBT. HBT was shown to alleviate inner ear immune injury in a rat model[20] and disturbance of equilibrium resulting from pregabalin in a rat model of neuropathic pain[57]. 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[58-60] when vertigo/dizziness occurs. Atractylenolide III in Atractylodes rhizome, triterpenes, and polysaccharides in Poria sclerotium, and triterpenoids in Alisma Tuber have antidiuretic effects[14,18,61,62], 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[63], 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[64], 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[59,65], which can prevent worsening of 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, similar to the pharmacological actions of SSRIs/SSNIs on serotonergic neurotransmission (5-HT-CRF pathway)[59,66-73], which increases ghrelin signaling and activates the BDNF/trkB/CREB pathway in the cerebral cortex and vestibular nucleus[67-71,74-76]. Thus, in PPPD patients, HBT is speculated 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[3,4], and is consistent with strategies 2 and 3. In addition, gastroesophageal vagal nerve activation by HBT[59,60] might produce feedback resulting in somatosensory suppression *via* the autonomic nervous system in the hypothalamus, anterior cingulate gyrus, and insular cortex[77-79], resulting in sensory reweighting to establish a balance between the systems and increased tolerance to the perceived 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 patients with autonomic dysfunction, body balance dysfunction related to vestibular (ACF), visual (ARF), or somatosensory (VFCF and AFCF) factors[41], unilateral canal paresis, 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 L/H 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 improve antecedent vestibular diseases and autonomic dysfunction modified by mood disorders. Therefore, our speculation regarding the mechanism of HBT for PPPD therapy (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 affect 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 adjunctive 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 diseases 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 have been approved as a cure for this condition. Hangebyakujututemmato (HBT) has been reported as a potential treatment for PPPD.

Research objectives

Our aim is to examine the feasibility of HBT for PPPD.

Research methods

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

Research results

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.

Research conclusions

HBT may be an effective adjunct in PPPD. We identified the HBT responders.

Research perspectives

According to our results and previous reports, it was predicted that several herbal ingredients in HBT might improve autonomic function and the CREB-BDNF pathway, resulting in sensory reweighting to establish a balance between the systems involved in PPPD.

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