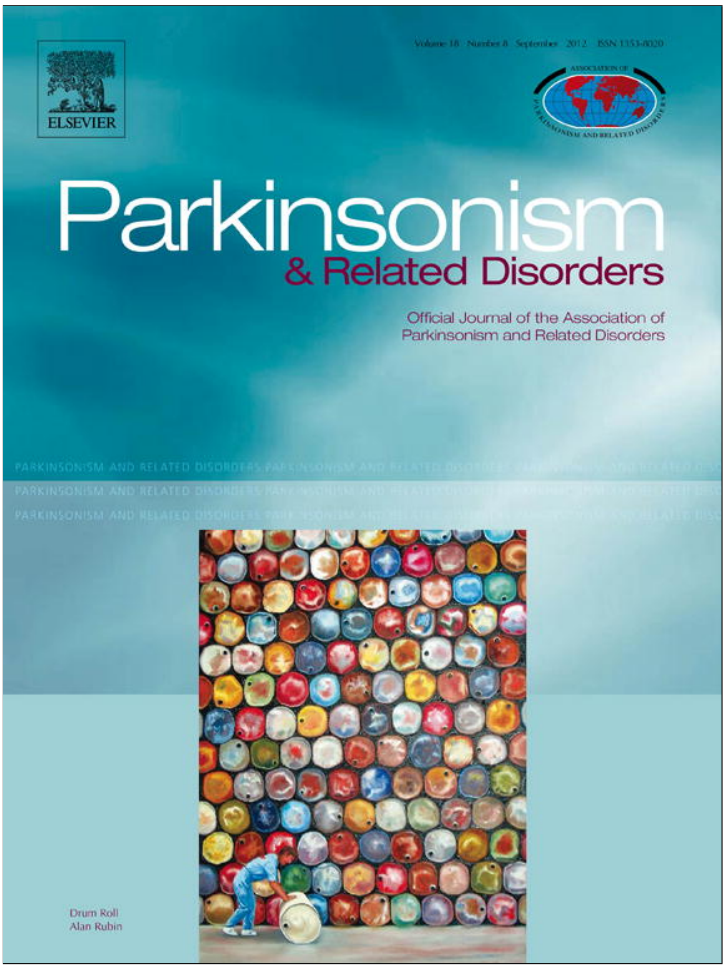

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Effectiveness of acupuncture and bee venom acupuncture in idiopathic Parkinson's disease

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ABSTRACT

This study aimed to explore the effectiveness of both acupuncture and bee venom acupuncture as adjuvant therapies for idiopathic Parkinson's disease.

We recruited 43 adults with idiopathic Parkinson's disease who had been on a stable dose of anti-parkinsonian medication for at least 1 month. They were randomly assigned to 1 of 3 groups: acupuncture, bee venom acupuncture, or control. All participants were assessed using the Unified Parkinson's Disease Rating Scale, the Parkinson's Disease Quality of Life Questionnaire, the Beck Depression Inventory, the Berg Balance Scale, and the time and number of steps required to walk 30 m. Treatment groups underwent stimulation of 10 acupuncture points using acupuncture or bee venom acupuncture twice a week for 8 weeks. The initial assessment was repeated at the completion of treatment. The control group did not receive any treatment.

Participants in the bee venom acupuncture group showed significant improvement on the Unified Parkinson's Disease Rating Scale (total score, as well as parts II and III individually), the Berg Balance Scale, and the 30 m walking time. When compared to the control group, the bee venom acupuncture group experienced significantly greater improvement on the Unified Parkinson's Disease Rating Scale. In the acupuncture group, the Unified Parkinson's Disease Rating Scale (part III and total scores) and the Beck Depression Inventory showed significant improvement. The control group showed no significant changes in any outcome after 8 weeks.

In this pilot study, both acupuncture and bee venom acupuncture showed promising results as adjuvant therapies for Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by the selective loss of dopaminergic neurons of the substantia nigra pars compacta, resulting in reduced striatal dopamine. Levodopa is the drug of choice in PD due to its ability to initially improve core symptoms by increasing basal ganglia dopamine activity. However, after 5 years of therapy, 50% of patients experience motor response complications, and the benefit from each dose becomes weaker ("wearing-off" fluctuations), more unpredictable ("on–off" fluctuations), and associated with involuntary movements (dyskinesias). In addition, patients continue to suffer from fluctuations in motor function that are inherent to the disease itself [1].

In light of the significant limitations of conventional therapy, interest is increasing in complementary and alternative therapies. It has been previously reported that 40% of patients with PD in the United States and Europe use complementary and alternative therapies, compared to 54% of patients in the United Kingdom, and an even higher percentage in Asia [2,3]. Acupuncture is one of the most popular alternative therapies used by patients with PD [2,3].

Acupuncture has been used to relieve PD-like symptoms in Asian countries for centuries. In some experimental studies, acupuncture has been demonstrated to possess neurotrophic and neuroprotective effects [4–6]. Neuroimaging studies using techniques such as single-photon emission computed tomography,

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positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been also conducted to identify the mechanisms of acupuncture's effects in PD [7–9]. Clinically, however, the therapeutic effect of acupuncture in PD remains under debate [2,10–12].

Bee venom acupuncture (BVA), which involves the injection of dilute bee venom into acupuncture points, is used in the treatment of disorders such as pain, arthritis, rheumatoid diseases, cancer, and skin diseases [13,14]. Recently, the anti-neuroinflammatory effect of bee venom has been investigated, and the possibility of its use in the treatment of neurodegenerative disorders has been suggested [15]. Doo et al. [16] and Kim et al. [17] found that bee venom effectively protected dopaminergic neurons against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity. To the best of our knowledge, however, there have been no studies on the effectiveness of BVA in PD.

The primary aim of this randomized, controlled, assessor-blind pilot study was to evaluate the effectiveness of BVA as an adjunctive treatment in adults with idiopathic PD (IPD), with a secondary aim of comparing the effectiveness of acupuncture with BVA.

2. Materials and methods

2.1. Ethics approval

This study was performed in accordance with the ethical standards of the Helsinki Declaration. The protocol was approved by the Institutional Review Board of our university hospital (KHNMC-OH-IRB-2010-004). Informed consent was obtained from all participants after they were given a full description of the study.

2.2. Patient recruitment and selection

This study took place between August 2010 to June 2011. We recruited subjects through the website and bulletin boards of a single hospital. Interested subjects contacted the study coordinator for further information. Potential subjects were then offered a formal in-person assessment.

2.3. Inclusion and exclusion criteria

We included adult patients with IPD who had been on a stable dose of antiparkinsonian medication for at least 1 month. The study neurologist diagnosed each patient with IPD based on symptoms, medications, and brain imaging. We excluded patients with severe previous or current psychiatric or organic brain disorders other than PD (including secondary Parkinsonism), atypical Parkinsonism, somatic diseases, alcohol abuse, or narcotic abuse. All patients were advised not to change any of their antiparkinsonian medications during the study period, and subjects with prescriptions that changed during the study period or those who skipped more than 5 of the total of 16 treatment sessions were eliminated from the study.

2.4. Study protocol

This pilot study was a randomized controlled clinical trial in which subjects were divided into 3 groups by block design randomization to receive acupuncture, BVA, or no treatment.

After randomization, all subjects were assessed by the Unified Parkinson's Disease Rating Scale (UPDRS), Parkinson's Disease Quality of Life Questionnaire (PDQL), Beck Depression Inventory (BDI), Berg Balance Scale (BBS), the time and number of steps required to walk 30 m. The assessor was blinded to group allocation. Patients in the treatment groups underwent stimulation of 10 acupuncture points using acupuncture or bee venom acupuncture twice a week for 8 weeks. The initial assessment was repeated at the completion of treatment. The control group did not receive any treatment during this period, but subsequently received acupuncture or BVA according to the study protocol twice a week for 8 weeks, followed by an additional full assessment.

2.5. Interventions

All acupuncture and treatments were performed by a single physician trained in traditional Korean medicine. Subjects in the treatment groups received stimulation with acupuncture or BVA at 10 acupuncture points (bilateral GB 20, LI 11, GB 34, ST36, and LR 3) twice a week for 8 weeks (16 total sessions). The acupuncture points were selected based on previous studies on PD [2, 10, 11]. In the acupuncture group, sterile, disposable, stainless steel acupuncture needles (diameter = 0.25 mm, length = 30 mm, Dongbang, Korea) were inserted into the points listed above at a depth of 1.0–1.5 cm and rotated at 2 Hz for 10 s to achieve *Deqi*, the sensation felt by the subject when the acupuncture needle is at the appropriate position for clinical efficacy, and the position was maintained for 20 min. In the BVA group, 0.1 ml bee venom diluted to 0.005% in distilled water (Yumil Farm, Korea) was injected into each point.

2.6. Skin testing for venom allergy

In the BVA group, a skin test was performed to determine if the subject was allergic to bee venom. An injection of 0.1 ml bee venom diluted to 0.005% in distilled water was performed at LI11; production of a wheal larger than 5 mm, a rash greater than 11 mm in diameter, or severe itching at the site within 15–20 min were considered a bee venom allergy, and the subject was excluded from the study.

2.7. Outcome measures

The primary outcome measure was the UPDRS total score. Secondary outcome measures were the sub-scores of UPDRS (parts I–V), PDQL, BDI, BBS, and the time and number of steps required to walk 30 m.

2.8. Statistical analysis

Data were expressed as medians of the lower and upper quartiles. The Wilcoxon signed-rank test and Kruskal–Wallis test were used to examine statistical significance using Statistical Package for Social Sciences for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Tukey's HSD post-hoc test was used to analyze data with equal variances, and Dunnett's T3 test was used to analyze data with unequal variances. A *P*-value less than 0.05 was considered significant.

3. Results

3.1. Baseline subject characteristics

A total of 89 people with PD contacted the trial coordinator to inquire about eligibility; 46 were excluded because they did not wish to participate, did not meet the inclusion criteria, or lived too far from the hospital. The remaining 43 patients with IPD were included in the study and randomized into 3 groups: acupuncture (15), BVA (14), or control (14). After 8 weeks of waiting, 6 subjects from the control group were reassigned to BVA (4) or acupuncture (2) groups (Fig. 1).

During the study, we excluded 4 patients in the acupuncture group, 5 patients in the BVA group, and 5 in the waiting group. We analyzed data from the remaining 35 patients (13 in the acupuncture group, 13 in the BVA group, and 9 in the waiting group) (Fig. 1). Subjects consisted of 13 men and 22 women, with a mean age of 58.40 ± 10.04 years and a mean duration of IPD of 5.97 ± 3.71 years. Their Hoehn and Yahr stages ranged from 1 to 3. There were no significant differences in any baseline characteristics between groups (Table 1).

3.2. Changes in assessment scores

As shown in Table 2, participants in the BVA group showed significant improvement on the UPDRS (total score, as well as parts II and III individually), the BBS, and the 30 m walking time. When compared to the control group, the BVA group improved significantly more on the UPDRS (total score, as well as parts II and III individually). In the acupuncture group, the UPDRS (part III and total scores) and the BDI showed significant improvement. The control group showed no significant changes in any outcome after 8 weeks.

3.3. Adverse events

Study subjects were encouraged to report all adverse events. There were no serious adverse events from the BVA or acupuncture treatments. One subject in the BVA group complained of itchiness and was eliminated from the study.

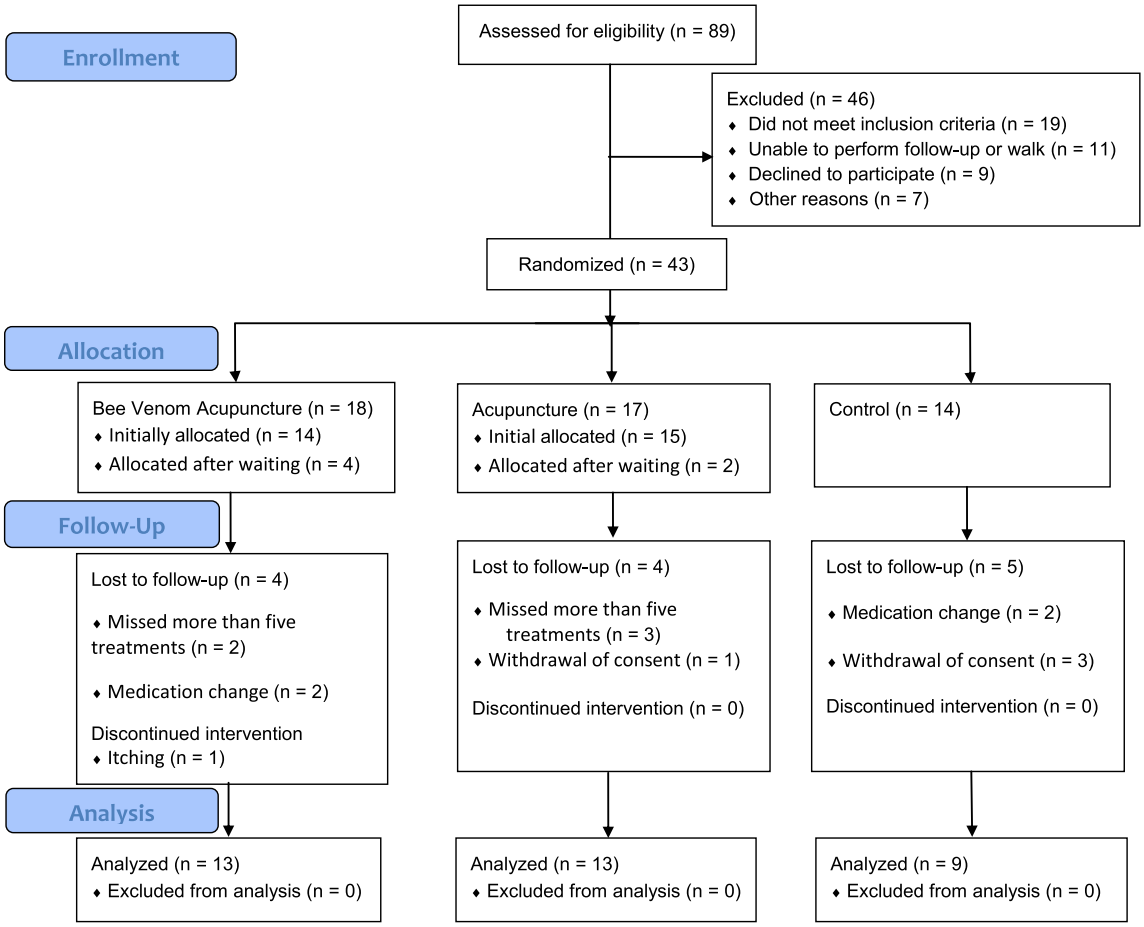

Fig. 1. Flow chart of patient recruitment.

4. Discussion

In this study, patients who underwent 8 weeks of twice-weekly BVA or acupuncture treatments showed significant improvement in motor symptoms (UPDRS part III) and total UPDRS score compared to their baseline assessments. In the BVA group, UPDRS part II, BBS and 30 m walking time also showed significant improvement compared with baseline scores, and UPDRS part II, part III, and total scores improved significantly compared with those in the control group. Although we attempted to compare the effects of acupuncture with BVA as adjunctive treatments for PD, there was no significant difference between treatment groups. Therefore, it remains unclear which may be more effective in PD.

Although several clinical studies have used acupuncture in patients with PD, few found significant improvement in motor symptoms. Shulman et al. [2] reported subjective improvement in

Table 1
Baseline patient characteristics.

	Bee venom ($n = 13$)	Acupuncture ($n = 13$)	Control ($n = 9$)	P-value
Gender, n (M/F)	5/8	5/8	3/6	
Age (years)	57.0 (49.0, 69.0)	55.0 (52.0, 66.0)	57.0 (48.0, 68.0)	0.912
Duration (years)	5.0 (2.0, 10.0)	6.0 (3.0, 9.0)	5.0 (4.0, 7.0)	0.943
Total UPDRS (I-V)	32.0 (21.5, 51.0)	40.0 (27.5, 53.0)	32.0 (20.5, 51.0)	0.718
UPDRS I	3.0 (1.5, 4.0)	3.0, (1.0, 3.5)	2.0 (1.0, 3.5)	0.728
UPDRS II	9.0 (6.0, 17.0)	11.0 (9.5, 17.0)	10.0 (6.0, 16.5)	0.631
UPDRS III	15.0 (10.0, 18.5)	17.0 (11.0, 22.5)	13.0 (8.0, 21.5)	0.763
UPDRS IV	5.0 (2.0, 10.0)	5.0 (4.5, 9.0)	5.0 (3.0, 11.5)	0.904
UPDRS V	1.5 (1.0, 1.75)	1.5 (1.0, 2.25)	1.0 (1.0, 1.75)	0.684
UPDRS VI	90.0 (75.0, 95.0)	90.0 (60.0, 90.0)	90.0 (65.0, 90.0)	0.712
BBS	55.0 (52.0, 56.0)	56.0 (54.0, 56.0)	55.0 (54.0, 56.0)	0.777
30-m walking time (sec)	27.69 (26.53, 29.98)	26.29 (25.14, 32.83)	27.78 (26.315, 32.125)	0.812
Steps to walk 30-m	49.0 (47.5, 55.0)	49.0 (46.5, 60.5)	51.0 (49.0, 61.5)	0.757
PDQL	144.0 (113.5, 149.5)	132.0 (94.5, 141.5)	130.0 (93.5, 146.5)	0.571
BDI	10.0 (5.5, 17.5)	17.0 (7.5, 31.5)	9.0 (7.5, 17.0)	0.308

Values are median (lower quartile, upper quartile) for the Kruskal–Wallis test.
UPDRS: Unified Parkinson's Disease Rating Scale; BBS: Berg Balance Scale; 30-m walking time: the time required to walk 30 m; Steps to walk 30 m: the number of steps required to walk 30 m; PDQL: Parkinson's Disease Quality of Life Questionnaire; BDI: Beck Depression Inventory.

Table 2
Changes in clinical outcomes in each group after eight weeks.

	Bee venom		Acupuncture		Control	
	Before	After	Before	After	Before	After
Total UPDRS	32.0 (21.5, 51.0)	24.0 (17.5, 35.0)[a,b]	40.0 (27.5, 53.0)	33.0 (21.0, 44.5)[a]	32.0 (20.5, 51.0)	38.0 (17.5, 53.5)
UPDRS I	3.0 (1.5, 4.0)	2.0 (0.5, 3.0)	3.0 (1.0, 3.5)	1.0 (1.0, 3.0)	2.0 (1.0, 3.5)	2.0 (0.5, 3.5)
UPDRS II	9.0 (6.0, 17.0)	7.0 (5.0, 11.5)[a,c]	11.0 (9.5, 17.0)	11.0 (6.0, 14.5)	10.0 (6.0, 16.5)	11.0 (5.5, 16.5)
UPDRS III	15.0 (10.0, 18.5)	10.0 (6.5, 10.0)[a,b]	17.0 (11.0, 22.5)	13.0 (6.5, 19.5)[a]	13.0 (8.0, 21.5)	13.0 (8.5, 23.5)
UPDRS IV	5.0 (2.0, 10.0)	6.0 (2.0, 8.5)	5.0 (4.5, 9.0)	5.0 (4.0, 9.5)	5.0 (3.0, 11.5)	6.0 (3.0, 11.5)
UPDRS V	1.5 (1.0, 1.75)	1.5 (1.0, 1.5)	1.5 (1.0, 2.25)	1.0 (1.0, 1.75)	1.0 (1.0, 17.5)	1.5 (1.0, 1.5)
UPDRS VI	90.0 (75.0, 95.0)	90.0 (80.0, 95.0)	90.0 (60.0, 90.0)	80.0 (65.0, 90.0)	90.0 (65.0, 90.0)	90.0 (70.0, 95.0)
BBS	55.0 (52.0, 56.0)	56.0 (55.5, 56.0)[a]	56.0 (54.0, 56.0)	56.0 (53.5, 56.0)	55.0 (54.0, 56.0)	56.0 (53.5, 56.0)
30-m walking time (sec)	27.69 (26.53, 29.98)	26.13 (24.65, 28.47)[a]	26.29 (25.14, 32.83)	27.04 (23.87, 30.44)	27.78 (26.31, 32.12)	27.69 (25.53, 35.31)
Steps to walk 30-m	49.0(47.5, 55.0)	50.0(45.0, 55.0)	49.0(46.5, 60.5)	49.0(43.5, 56.0)	51.0(49.0, 61.5)	49.0(47.0, 65.0)
PDQL	144.0(113.5, 149.5)	148.0(119.5, 162.5)	132.0(94.5, 141.5)	137.0(113.0, 156.0)	130.0(93.5, 146.5)	132.0(121.0, 148.5)
BDI	10.0 (5.5, 17.5)	9.0 (4.0, 18.0)	17.0 (7.5, 31.5)	12.0 (5.0, 18.5)[a]	9.0 (7.5, 17.0)	8.0 (7.0, 17.5)

Values are median (lower quartile, upper quartile).
UPDRS: Unified Parkinson's Disease Rating Scale, BBS: Berg Balance Scale, 30 m walking time: the time required to walk 30 m; Steps to walk 30 m: the number of steps required to walk 30 m; PDQL: Parkinson's Disease Quality of Life Questionnaire; BDI: Beck Depression Inventory.
Before: baseline; after: after eight weeks.
[a] $P < 0.05$ in Wilcoxon Signed Rank Test versus baseline.
[b] Indicates a statistical difference between each treatment group and the control group by Tukey's HSD post-hoc test ($P < 0.05$).
[c] Indicates a statistical difference between each treatment group and the control group by Dunnett's T3 test ($P < 0.05$).

some symptoms such as tremors, handwriting, difficulty walking and sleep; however, there were no significant changes in motor scores compared to baseline. In another study of patients with IPD, Cristian et al. [12] reported that a trend toward significant improvement was noted in the PDQL subsections for Activities of Daily Living and depression, as well as for the PDQ-8 Summary Index score and the UPDRS, although no outcomes reached statistical significance. In contrast, we found that both acupuncture and BVA significantly improved motor symptoms in patients with IPD.

Currently, the mechanism underlying the effects of acupuncture on motor symptoms in PD is unclear. Nonetheless, both acupuncture and BVA have demonstrated neuroprotective effects. In MPTP- or 6-hydroxydopamine-induced models of PD, acupuncture inhibited microglial activation and inflammation [4,5], promoted the expression of brain-derived neurotrophic factor and its receptor tyrosine kinase B [5,18], and attenuated oxidative stress to dopaminergic neurons [19]. BVA was also reported to have protective effects on dopaminergic neurons against MPTP toxicity [16].

Neuroprotective action may delay the progress of PD [20,21], but it is insufficient to explain the motor improvement observed in the present study. The motor symptoms of PD (tremor, rigidity, and bradykinesia) are related to striatal dopamine depletion, and therefore increasing striatal dopamine has been thought to be the best course of therapy. Several studies have been carried out to test whether acupuncture could increase striatal dopamine levels; however, there is no evidence that acupuncture has such an effect [7,22].

On the other hand, increasing evidence suggests a poor relationship between the dopamine content of the striatum and improvement in motor symptoms during treatment [22,23]. Studies of parkinsonian movement disorders revealed that they are often associated with abnormalities in γ-aminobutyric acid (GABA) neuron activity in the substantia nigra pars reticulata [24]. Jia et al. [22] reported that electro-acupuncture improved motor function in a hemiparkinsonian rat model induced by unilateral transection of the medial forebrain bundle. The authors found that acupuncture normalized midbrain GABA levels without increasing striatal dopamine, suggesting that acupuncture improves motor impairment in PD by increasing GABAergic inhibition in the output structure of the basal ganglia.

Other studies have also investigated acupuncture's therapeutic mechanisms in PD. An fMRI study suggested that acupuncture improves motor function in patients with PD via the basal ganglia-thalamocortical circuit, while a PET study found that acupuncture in combination with Madopa increased cerebral glucose metabolism in PD patients [8,9]. It is unclear if any of these mechanisms are associated with our results. However, if acupuncture or BVA affects PD through a different mechanism from that of levodopa, it could be expected to show a synergic effect with levodopa as an adjuvant therapy.

Acupuncture also significantly improved BDI in this study. This result is similar to the study performed by Shulman [2]. Depression, one of the non-motor symptoms of PD, is highly prevalent in PD patients (40–50%), but is often overlooked in favor of the disease's motor symptoms [25].

The effectiveness of acupuncture for depressive disorders has been demonstrated in several clinical trials [26]. In relation to these results, the mechanism by which acupuncture affects depression-related behavior was found by some recent studies to include significant changes in hippocampal metabolites [27], reduction in corticosterone and adrenocorticotropin plasma hormone levels and arginine vasopressin immunoreactivity in the hypothalamic paraventricular nucleus of maternal separation rats [28], and effects on glial atrophy in the hippocampus [29]. Although the etiology and mechanisms of depression in PD and non-PD patients may differ, treatment of these two groups is similar in clinical practice, and antidepressants for non-PD patients are known to improve depression in PD patients [30]. In our study, we found that acupuncture may also improve depression in PD patients. Further study of the mechanism of acupuncture's apparent effectiveness in treating depression in patients with PD is warranted.

This pilot study has several limitations, most notably its small sample size. Although no definite conclusion can be drawn from our results, the patients in our trial who underwent either acupuncture or BVA had significant improvement in a variety of symptoms compared to control subjects, indicating a potential benefit of these treatments as adjuncts in PD. Other limitations of this study include lack of long-term follow-up and the inclusion of subjects with similar stages of PD. Thus a larger study with long-term follow-up is needed to replicate our results. Many questions remain regarding the usefulness of acupuncture and BVA in PD: When should treatment start? How long should these therapies be given? How can we best combine strategies? Further studies will be necessary to address these issues.

Author roles

Seung-Yeon Cho, K.M.D., Ph.D.: Intervention, writing of the first draft.

So-Ra Shim, K.M.D.: Assessment outcomes, statistical analysis.

Hak Young Rhee, M.D., Ph.D.: Diagnosis of IPD.

Hi-Joon Park, K.M.D., Ph.D.: Research conception, statistical analysis design.

Woo-Sang Jung, K.M.D., Ph.D.: Statistical analysis review and critique.

Sang-Kwan Moon, K.M.D., Ph.D.: Statistical analysis review and critique.

Jung-Mi Park, K.M.D., Ph.D.: Manuscript review and critique.

Chang-Nam Ko, K.M.D., Ph.D.: Research organization.

Ki-Ho Cho, K.M.D., Ph.D.: Manuscript review and critique.

Seong-Uk Park, K.M.D., Ph.D.: Research conception, randomization, manuscript review and critique.

Conflicts of interest

All authors declare no conflicts of interest.

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