Randomized, Controlled Trial of Acupuncture for Fatigue in Parkinson’s Disease

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ABSTRACT: Background: Fatigue is a common and debilitating nonmotor symptom of PD. Because preliminary evidence suggests that acupuncture improves fatigue in other conditions, we sought to test its efficacy in PD. Methods: Ninety-four PD patients with moderate-to-high fatigue were randomized to receive 6 weeks of biweekly real or sham acupuncture. The primary outcome was change on the Modified Fatigue Impact Scale at 6 weeks. Secondary outcomes included sleep, mood, quality of life, and maintenance of benefits at 12 weeks. Results: Both groups showed significant improvements in fatigue at 6 and 12 weeks, but with no significant between-group differences. Improvements from baseline in mood, sleep, and quality of life were noted without between-group differences. Overall, 63% of patients reported noticeable improvements in their fatigue. No serious adverse events were observed. Conclusions: Acupuncture may improve PD-related fatigue, but real acupuncture offers no greater benefit than sham treatments. PD-related fatigue should be added to the growing list of conditions that acupuncture helps primarily through nonspecific or placebo effects. © 2016 International Parkinson and Movement Disorder Society

Key Words: Parkinson’s disease; fatigue; acupuncture; randomized, controlled trial

Fatigue affects approximately half of all Parkinson’s disease (PD) patients, and one third report fatigue as their single most disabling symptom.1-4 A recent meta-analysis found insufficient evidence to support the use of any available pharmacological or nonpharmacological therapies.5 This is consistent with clinical practice where response to currently available medications (e.g., stimulants) is frequently suboptimal or limited by side effects. Use of alternative medicines, including acupuncture, has grown in Western societies and among PD patients.6 Preliminary evidence suggests that acupuncture may improve chronic fatigue syndrome and cancer-related fatigue, but it has not been tested for PD-related fatigue.7-9 Thus, our primary aim was to determine whether a 6-week course of acupuncture could improve PD-related fatigue. Because past studies of acupuncture for PD motor symptoms were limited by methodological issues, we conducted a rigorous and adequately powered randomized, controlled trial (RCT).9

Patients and Methods

Participants

Participants were recruited from the University of Colorado Hospital (Aurora, CO) and Denver Health Medical Center (Denver, CO) movement disorders clinics, referrals from community neurologists, and the Parkinson’s Association of the Rockies’ support...
groups and newsletter. Inclusion criteria included: UK Brain Bank criteria for probable PD; age 40 to 99 years; fluent in English; stable medication use for 30 days; and self-reported moderate or severe fatigue using the International Parkinson and Movement Disorder Society UPDRS fatigue item. Patients with DBS or on medications for fatigue (e.g., stimulants) were included provided they had ongoing fatigue. Exclusion criteria included dementia or a score below 24 on the Montreal Cognitive Assessment (MoCA); presence of another medical condition expected to produce fatigue; active depression or Hospital Anxiety and Depression Scale (HADS) depression subscale score greater than 10; presence of an untreated sleep disorder; or exposure to acupuncture within the past 6 months. This study was approved by the Colorado Multiple Institutional Review Board, and written informed consent was obtained from all participants. This trial was registered with ClinicalTrials.gov (NCT01360229).

Screening and Randomization

We performed a prescreening checklist by phone followed by an in-person assessment. Eligible participants were randomized in a 1:1 fashion without stratification to real or sham treatment using permuted blocks. Acupuncturists were provided a code-linking group assignment to study identification number. All other study team members were blind to group assignment.

Intervention

Treatment consisted of twice-weekly sessions at least 1 day apart for 6 weeks using a fixed-point prescription based on traditional Chinese medicine theory and past articles in PD and fatigued populations. Participants lay supine on the acupuncture table and were blindfolded. For real treatment, acupuncture needles (Seirin, 36-gauge, 1-inch) were inserted to a depth of 0.5 to 1 cm in the following order: governing vessel (GV) 20, GV 24, conception vessel 6, right large intestine (LI) 10, right heart (HT) 7, right stomach (ST) 36, right spleen (SP) 6, left LI 10, left HT 7, left ST 36, and left SP 6. For each point, the needle was twisted three times to the right. After 30 minutes, needles were removed in the same order as they were inserted, dropping needles into a sharps container every three removals.

We utilized a previously validated sham procedure in which a sharp, round toothpick in a guide tube was placed on the sham point and tapped on the skin. The toothpick was twisted three times to the right. Toothpicks were “inserted” in the same order as the real protocol using nonacupuncture points, located 0.5 in lateral to the real acupuncture point or to the right for midline points. Acupuncturists “removed” toothpicks by slowly pressing a toothpick into the sham point and quickly removing it in the same order they were inserted. Toothpicks were discarded three at a time into a sharps container to mimic sounds heard with real treatment. For both real and sham treatments, all points were swabbed with cotton after needle/toothpick removal so that subjects would not know whether they had any minor bleeding.

Primary Outcome

Our primary outcome was change from baseline on the Modified Fatigue Impact Scale (MFIS) at 6 weeks. The MFIS is a 21-item self-report scale that rates the impact of fatigue on various functions and includes a total score (primary outcome) as well as cognitive, physical, and psychosocial subscores. The MFIS has been validated for use in PD and may be more responsive than other commonly used fatigue scales.

Secondary Outcomes

Motor function was quantified using the motor subsection of the UPDRS. Mood was assessed using the HADS. Sleep quality and excessive daytime
somnolence were assessed using the Parkinson’s Disease Sleep Scale (PDSS) and Epworth Sleepiness Scale (ESS).\textsuperscript{19,20} Apathy was assessed using the Apathy Evaluation Scale (AES).\textsuperscript{21} Quality of life (QOL) was assessed using the 39-item Parkinson Disease Questionnaire (PDQ-39).\textsuperscript{22} Patients, investigators, and caregivers completed a Clinical Global Impression of Improvement scale at each visit, rating overall improvement on a 7-point scale from “very much improved” to “very much worse.”\textsuperscript{23} Patients were queried on their perceived group assignment to test blinding adequacy.

### Results

#### Baseline Characteristics

From November 2010 to November 2013, a total of 115 persons were screened and 94 qualified and underwent randomization (see Fig. 1 for The Consolidated Standards of Reporting Trials [CONSORT] diagram). Table 1 shows the demographic and clinical characteristics of our cohort.

Eighty-nine participants completed the assigned intervention and provided complete data on outcome measures at both the 6-week follow-up (primary outcome) and 12-week washout visits. Three patients took stimulants during the study. Groups were not statistically different on baseline measures, with the exception of UPDRS Motor score (sham group was higher) and PDSS (real group was higher). Compliance with the treatment protocol was high (99.5% of study treatments completed) and did not differ between groups (Fisher’s exact test; \( P = 0.37 \)).

#### Primary Outcome

Table 2 outlines baseline and 6-week values for the MFIS and its subscales. The acupuncture and sham-treated groups demonstrated significant improvements in the MFIS and all subscores at 6 weeks, but this improvement did not differ significantly between

### Statistical Analysis

We estimated that a sample size of 45 participants per group would provide at least 80% power at a significance level of 0.05 to detect a between-group difference of 10 points on our primary outcome measure, a value reported to be clinically significant in multiple sclerosis, or an effect size of approximately 0.6 mean/standard deviation (SD).\textsuperscript{16,24,25} Groups at baseline were compared on ordinal and interval measures using Wilcoxon’s rank-sum tests and on dichotomous measures using chi-square testing. We examined within-group changes between baseline and 6 weeks using paired \( t \) tests. We used analysis of covariance (ANCOVA) modeling to examine the effect of group assignment on fatigue and secondary outcomes. An intent to treat (ITT) was also conducted using the last observation carried forward. All testing was two-sided using a level of significance of 0.05 using SAS software (version 9.3; SAS Institute Inc., Cary, NC).
TABLE 2. Outcome measures at baseline and 6 weeks and between-group differences

<table>
<thead>
<tr>
<th></th>
<th>Acupuncture</th>
<th>Sham</th>
<th>Change P Value</th>
<th>Mean ± SD Week 1</th>
<th>Mean ± SD Week 6</th>
<th>ANCOVA P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFIS: Total</td>
<td></td>
<td></td>
<td></td>
<td>Mean ± SD Week 1</td>
<td>Mean ± SD Week 6</td>
<td>From ANCOVA</td>
</tr>
<tr>
<td></td>
<td>48.7 ± 10.5</td>
<td>50.0 ± 12.9</td>
<td>0.0001</td>
<td>35.5 ± 14.7</td>
<td>34.1 ± 17.5</td>
<td>0.4388</td>
</tr>
<tr>
<td>MFIS: Physical</td>
<td>23.7 ± 5.8</td>
<td>24.0 ± 6.2</td>
<td>0.0001</td>
<td>17.9 ± 7.1</td>
<td>16.2 ± 8.0</td>
<td>0.1881</td>
</tr>
<tr>
<td>MFIS: Cognitive</td>
<td>20.7 ± 6.6</td>
<td>21.6 ± 7.1</td>
<td>0.0001</td>
<td>14.6 ± 7.8</td>
<td>14.9 ± 8.7</td>
<td>0.9222</td>
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<tr>
<td>MFIS: Psychosocial</td>
<td>4.3 ± 1.4</td>
<td>4.4 ± 1.7</td>
<td>0.0001</td>
<td>3.0 ± 1.7</td>
<td>3.0 ± 2.0</td>
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</tr>
<tr>
<td>UPDRS Motor</td>
<td>21.6 ± 7.8</td>
<td>26.7 ± 11.1</td>
<td>0.7712</td>
<td>21.3 ± 8.8</td>
<td>25.9 ± 11.7</td>
<td>0.2072</td>
</tr>
<tr>
<td>PDQ-39 Total</td>
<td>27.4 ± 10.0</td>
<td>31.2 ± 14.9</td>
<td>0.0002</td>
<td>21.6 ± 12.2</td>
<td>24.5 ± 15.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>5.7 ± 3.0</td>
<td>7.0 ± 4.0</td>
<td>0.0876</td>
<td>5.0 ± 3.3</td>
<td>5.7 ± 4.1</td>
<td>0.0003</td>
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<tr>
<td>HADS Depression</td>
<td>5.7 ± 2.1</td>
<td>5.7 ± 3.1</td>
<td>0.0397</td>
<td>5.0 ± 2.3</td>
<td>5.2 ± 3.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>PDSS</td>
<td>101.7 ± 19.0</td>
<td>89.7 ± 23.6</td>
<td>0.1026</td>
<td>107.0 ± 20.4</td>
<td>100.4 ± 21.4</td>
<td>0.0003</td>
</tr>
<tr>
<td>ESS</td>
<td>12.0 ± 3.7</td>
<td>11.8 ± 4.9</td>
<td>0.0010</td>
<td>10.4 ± 4.0</td>
<td>9.0 ± 4.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>AES</td>
<td>13.0 ± 6.1</td>
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<td>0.0159</td>
<td>11.3 ± 5.3</td>
<td>11.5 ± 6.7</td>
<td>0.0552</td>
</tr>
</tbody>
</table>

significant improvements, including QOL and sleepiness.

Secondary Outcomes

Table 2 outlines baseline and 6-week values for secondary outcomes. There were no significant differences between groups for any secondary outcome measure, but several measures did show statistically significant improvements, including QOL and sleepiness.

Maintenance of Benefits

Figure 2 shows the time course of MFIS values for the real and sham treatment groups. MFIS values were significantly different from baseline beginning at 3 weeks for both groups and remained significantly different at 12 weeks, with no between-group differences.

Adverse Events and Blinding Adequacy

The only potential study-related adverse event was increased constipation in 1 participant receiving real acupuncture whose regular pattern of bowel movements resumed 1 week after stopping acupuncture. Participants were queried at the 6-week time point regarding what group they thought they were in, and there were no between group differences in patients’ perceptions of group assignment consistent with effective blinding (chi-square, \( P = 0.51 \)).

FIG. 2. Change in Total MFIS scores over time by group. Error bars indicate standard error.
Discussion

We found PD patients with moderate-to-high self-reported fatigue experienced improvements in fatigue following a 6-week course of acupuncture and that improvements were similar for real and sham acupuncture. Acupuncture was safe and well tolerated. These results suggest that acupuncture may improve PD-related fatigue, but that acupuncture likely confers benefit through placebo or other nonspecific effects. Similar results from multiple rigorously conducted RCTs of acupuncture for other conditions suggest that specific point placement is not essential to acupuncture’s mechanism for most conditions studied to date.27

Many of our patients had failed or were currently on medications for fatigue with minimal clinical benefit, and we specifically excluded patients with depression or sleep disorders to avoid potential confounding effects of these conditions on fatigue. We thus feel that benefits obtained in this RCT are reflective of patients observed in clinical practice who are frequently refractory to available treatments and have been screened and treated for potential secondary causes of fatigue.

The interpretation of the results of RCT’s for acupuncture is complex and the subject of some controversy. The benefits of acupuncture may be attributed to specific effects from the acupuncture treatment (e.g., needle placement and technique), nonspecific effects of the acupuncture procedure (e.g., physical contact with acupuncturists, relaxation, and focusing on the body), study-related effects (e.g., reporting biases, regression to the mean), and classic placebo effects (which may be greater for placebo acupuncture than placebo pills).30,32 More complex study designs, including sham needles allowing for true double blinding, and use of wait-list controls have been proposed to better distinguish these effects, but also have limitations.23 Given the relative safety of acupuncture, it has been argued that as long as benefits are observed, it does not matter whether they are from placebo effects.34 Others argue that the failure of numerous studies to find any specific benefit of acupuncture argues against recommending its use in clinical practice.35 We refer to readers to draw their own conclusions regarding whether to recommend this treatment for PD-related fatigue.

Limitations of this study include lack of a wait-list, usual care, or prospective control arm, which limits our ability to determine whether benefits resulted from some aspects of the acupuncture procedure, placebo effects, or simply study participation. We did not include a wait-list control arm because fatigue tends to be a stable symptom in PD and wait-list control designs have their own limitations, including an inability to blind the wait-list group and negative expectancy effects, which may give false confidence in attributing intervention benefits.36 Participants interested in this study were highly educated and may have had a personal interest or experience with acupuncture, thus potentially biasing results. Finally, it is possible that use of fixed-point acupuncture may underestimate its effects given that points are typically individualized in clinical practice.

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References