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Commentary

Acupuncture for motor symptom improvement in Parkinson's disease and the potential identification of responders to acupuncture treatment

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1. Summary of Focal Article

1.1. Focal Article

Wang F, Sun L, Zhang XZ, Jia J, Liu Z, Huang XY, Yu SY, Zuo LJ, Cao CJ, Wang XM, Zhang W. Effect and Potential Mechanism of Electroacupuncture Add-On Treatment in Patients with Parkinson's Disease. Evid Based Complement Alternat Med. 2015;2015:692795. doi: 10.1155/2015/692795. Epub 2015 Aug 13[1]

1.2. Aim

The authors aimed to evaluate the effectiveness of electroacupuncture (EA) and explore its mechanisms in Parkinson's disease (PD) patients when used as an adjunctive therapy to conventional drugs.

1.3. Design

This study was a randomized, controlled (EA + drug vs. drug alone), assessor-blind, single-center, pilot trial.

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1.4. *Setting*

PD patients were recruited from May 2011 to May 2012 in the Department of Geriatrics and Neurology of Beijing Tiantan Hospital at Capital University.

1.5. *Participants*

Fifty PD patients using a stable dosage of anti-PD medication for at least two months without adverse effects were recruited. Patients were diagnosed by a neurologist according to the UK Parkinson's Disease Society Brain Bank criteria[2]. Patients with Parkinson plus syndrome or secondary Parkinson syndrome were not included.

Thirty patients were allocated to the treatment group (EA + drug). Twenty patients were allocated to the control group (drug only). During the clinical trial period, patients were not allowed to change their medication. Two patients dropped out due to PD medication changes.

1.6. *Intervention*

Needles 0.25 mm in diameter and 40 mm in length (Huatuo) were inserted into the following 6 acupoints based on previous studies: [3,4] bilateral GB20 (Pungji) and LI4 (Hapgok), and central GV16 (Pungbu) and GV14 (Daechu). The needles were stimulated using the following parameters for 30 minutes: 9 V, 1 A, 9 W, and 100 Hz (KWD-808-II; Yingdi, China). One acupuncture treatment course is composed of 10 sessions that occur every 3 days. Two treatment courses, equating to a total of 20 sessions of acupuncture treatment, were performed over 2 months. Participants who skipped more than 2 sessions of treatment were eliminated from the trial.

1.7. *Main Outcome Measures*

1.7.1. *Assessment schedule*

Assessments were performed 12 hours after the latest intake of PD medication. Treatment group patients were assessed after the completion of the entire EA treatment course. Control group patients were assessed 2 months after the baseline assessment date.

1.7.2. *Motor symptoms and motor complications*

The following items from the Unified Parkinson's Disease Rating Scale (UPDRS) III were used: total score, items 20 and 21 (tremor), item 22 (rigidity), and items 23-26 (bradykinesia). Hoehn–Yahr (H-Y) stage ratings were used to indicate the severity of PD and the UPDRS IV was used to assess motor complications.

1.7.3. *Non-motor symptoms*

Non-motor symptoms were assessed using the following tests: Nonmotor Symptoms Quest (NMSQ), including the Montreal Cognitive Assessment (MoCA); Mini-Mental State Examination (MMSE) for the assessment of cognitive function; Hamilton

Depression Scale (HAMD) 24-item test for the assessment of depression, Hamilton Anxiety Scale (HAMA) 14–item test for the assessment of anxiety, and Pittsburgh Sleep Quality Index (PSQI) for the assessment of sleep quality. [1]

1.7.4. *Activity of Daily Life (ADL) and Quality of Life (QOL)*

The UPDRS II and the ADL scale were used to assess ADL. QOL was evaluated using the Parkinson's Disease Quality of Life Questionnaire (PDQ) 39 item test.

1.7.5. *Neuroinflammatory factors and Neurotransmitters in Serum*

The following neuroinflammatory factors were measured: nitric oxide (NO), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and prostaglandin (PG) E2.

The following neurotransmitters were measured: dopamine (DA), acetylcholine (Ach), norepinephrine (NE), and 5-hydroxytryptamine (5-HT).

1.8. *Main Results*

1.8.1. *Comparison between treatment and control groups*

The UPDRS III score changes were significantly different before and after treatment. The change in the UPDRS III score was 4.9 ± 4.8 in the treatment group and 2.3 ± 3.0 in the control group. The change in the PSQI was 1.0 (0.0-2.0) in the treatment group, which was significant, while it was 0 in the control group. However, the H-Y stage, HAMD, HAMA, MMSE, and MoCA were not different between the two groups. The only biomarker that was significantly different following the treatment was the NO level (treatment group, 53.18 [6.42-64.51]; control group, 80.49 [62.15-107.57]).

1.8.2. *Within-group comparisons (before vs. after comparison in the treatment group)*

The motor symptoms evaluated using the UPDRS III score (25.6 ± 2.8 to 20.6 ± 2.7), and the tremor (4.9 ± 4.4 to 3.4 ± 3.9), rigidity (4.6 ± 3.4 to 3.6 ± 3.2), and bradykinesia (9.0 ± 6.3 to 7.4 ± 5.9) sub-items were significantly improved following treatment. Subgroup analysis revealed that the UPDRS III scores were decreased in patients with rigidity-bradykinesia type or mixed type PD, but not in those with tremor type PD. UPDRS III scores of patients with mild severity group were significantly improved (20.2 ± 2.6 to 14.7 ± 2.0), whereas those with moderate severity group did not show the significant improvement (33.5 ± 3.9 to 29.1 ± 4.1). The non-motor symptoms assessed using the PSQI and HAMD were improved, but no improvements were seen in other variables.

1.9. *Authors' conclusion:*

The motor symptoms of PD were significantly decreased by the addition of EA to standard treatment. These improvements were measured using the UPDRS III score and were especially evident in patients with mixed type or rigidity-bradykinesia type PD and in those with mild PD symptoms. EA treatment also improved the quality of sleep and depression in PD patients. Elevated NO levels may be a possible mechanism underlying the effects of EA.

2. Comment/Critique

The focal article indicates that EA improves motor symptoms, as assessed by the UPDRS III, and a non-motor symptom (quality of sleep), as measured by the PSQI. Several previous reports on the use of acupuncture did not indicate motor symptom improvement following this treatment. [5,6] However, positive reports on the use of acupuncture for PD treatment are increasing. Cho et al., [3] reported that 16 sessions of acupuncture or bee venom treatment improve the UPDRS III score in treated patients in comparison to patients in the no treatment control group in a 3-arm pilot randomized controlled trial. In another prospective open-label study, 11 participants underwent 12 consecutive weeks of conventional treatment and 12 weeks of conventional treatment combined with acupuncture and bee venom treatment. UPDRS II and III scores were significantly improved in the combined treatment phase compared to the conventional treatment phase. [7] In another randomized study, 36 sessions of adjunctive acupuncture therapy combined with western medication over 18 weeks led to a higher UPDRS total score improvement ratio (55% vs. 15%, p = 0.019) compared to medication-only group. [8] Acupuncture is also shown to have long-term effects. Patients in an L-dopa-only group (control group) and those in an L-dopa and acupuncture combination group (treatment group) were followed for 60 months. Patients in the treatment group received acupuncture treatment 2 to 4 times a month. Over the course of 5 years, UPDRS III scores worsened by 18.2 ± 9.8 points in the control group, but the only worsened by 11.9 ± 6.8 points in the treatment group (p = 0.043). [9] A recent meta-analysis of combined traditional east Asian medicine therapies, including acupuncture, moxibustion, herbal medicine, patent medicine, manual therapy, and qigong indicated that these treatments improved the UPDRS III score by 2.45 points [95% confidence interval (CI) (2.03 to 2.86)] and diminished 38% of the side effects associated with conventional drugs [risk ratio, 0.62 95% CI (0.40-0.96)]. [10]

The original focal article contains a considerable amount of discussion regarding the mechanisms underlying the effects of acupuncture in PD treatment. There are several articles discussing these mechanisms. An original article points to GABA activity in the substantia nigra as a factor mediating changes in motor symptoms, suggests NE and 5-HT decreases as factors underlying changes in depression, and DA changes as factors mediating changes in the incidence of sleep disorders. [1] However, in the focal article, there were no significant differences in these markers between the treatment and control groups, except for changes in serum NO levels. There were only within-group before and after differences in several of the neuroinflammatory factors and neurotransmitters. The authors thus failed to find a possible mechanism underlying the effects of EA treatment in patients with PD in this trial. What is more interesting in this article is that it identifies potential responders to EA treatment in PD. In this article, the mild severity group (H-Y stage 1 to 2) showed significant improvement after treatment. This effect was not observed in the moderate severity group (H-Y stage 2.5 to 3). This indicates that early EA treatment in PD may be helpful in alleviating motor symptoms. In a previous study, H-Y stage and age were predictive of the effects of integrated Chinese and western therapy as evaluated using the UPDRS III score. [11] The authors thus hypothesize that the severity of PD is a determinant of EA treatment response. Another subgroup analysis revealed that participants with tremor type PD did not improve following treatment. However those with rigidity–bradykinesia type or mixed type PD showed improvements after EA treatment. This indicates that the EA effect may not be the same in the different subtypes of the disease. These hypotheses may be supported by several observational studies. Observational studies are appropriate when designing feasible clinical trial protocols with large sample sizes. [12] There are insufficient resources, such as funding and manpower, for acupuncture research. As a result, there will not be any well-designed research exploring the response to acupuncture in the foreseeable future. However, knowing the response to acupuncture is a very important factor in designing appropriate clinical trial protocols and is a critical factor in the success of such clinical trials. A retrospective chart review or a retrospective cohort study using national health insurance data will be helpful in identifying patient who will improve following acupuncture treatment. Thus, the most valuable discovery of this focal article is the potential identification of responders to this treatment. I recommend that the authors define the responder and the non-responder group and compare baseline characteristics, severity, symptom subtype, and the levels of neuroinflammatory factors and neurotransmitters between these groups despite the small sample size.

This article indicates that acupuncture improves motor symptoms and quality of sleep in patients with PD. Lower NO levels in the treatment group indicate that acupuncture suppresses neuroinflammation, a hypothesis that should be tested by further research. The most interesting aspect of the focal article is the potential identification of responders to acupuncture treatment. At this point, more observational studies are needed, and not clinical trials, to study the characteristics of acupuncture treatment responders with PD.

Conflicts of Interest

None declared.

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