Is acupuncture effective against pain in patients with Parkinson's disease? A randomized controlled study

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ABSTRACT

Aim: To investigate the efficacy of acupuncture application in the treatment of neck pain of musculoskeletal origin in patients with Parkinson's disease (PD).

Methods: Forty-five patients were screened, of whom 40 were enrolled and 29 completed the study. The patients were divided into two groups, each consisting of 20 individuals. The acupuncture group (AG) received acupuncture therapy in addition to neck exercises, while the control group (CG) performed only neck exercises. Both groups were enrolled in an exercise program, every day of the week for five weeks. The AG also received 10 sessions of acupuncture, twice weekly. The Hoehn and Yahr Scale, the Visual Analog Scale (VAS), the Movement Disorder Society Unified Parkinson's Disease rating Scale-I (MDS-UPDRS-I), a Health Assessment Questionnaire (HAQ), and the Neck Disability Index (NDI) were applied as data collection tools before and at the end of treatment.

Results: Significant improvement was determined in both groups in post-treatment VAS, MDS-UPDRS-I, HAQ, and NDI values compared to pre-treatment ($p<0.05$). The improvement in VAS, MDS-UPDRS-I, HAQ, and NDI values was significantly greater in AG than in CG ($p<0.05$).

Conclusion: With its local and systemic effects, acupuncture is a safe procedure capable of use for analgesia. However, further randomized, placebo-controlled studies will permit a more detailed evaluation of its therapeutic efficacy.

Key words: Parkinson's disease, acupuncture, exercise, neck pain.

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Introduction

Parkinson's disease (PD) is a chronic, progressive, degenerative movement disorder characterized by motor and non-motor findings, the incidence of which increases with age [1, 2].

The principal cardinal motor findings during the course of the disease are rigidity, resting tremor, postural instability, gait disturbance, and bradykinesia characterized by a progressive decrease in the speed and amplitude of repetitive movements. In addition to these findings, secondary motor symptoms such as bradymimia, dysarthria, and associated movement in the arms also accompany the course of the disease [3, 4].

Non-motor findings can also develop in PD, including psychiatric findings, gastrointestinal

function disorders, autonomous nervous system disorders, and sensorial function disorders such as impaired pain perception. Non-motor symptoms can significantly impact patient freedom by affecting the quality of life in PD. They also become more dominant in the advanced stages of the disease and can represent difficulty in terms of treatment [5, 6]. The incidence of patients reporting at least one non-motor symptom in PD in previous studies is close to 100% [7].

Pain-related disability, one of the non-motor findings of PD, is a symptom that reduces the quality of life. The reported pain rate in patients with PD is between 40-83% [8, 9]. In approximately 62% of patients with PD, it was determined that the pain became chronic [6]. Pain is the first symptom in 5.5% of patients. [10]. There is no consensus on the assessment and classification of pain in PD. Pain symptoms associated with PD have in recent years been classified as musculoskeletal pains, radicular/neuropathic pain, dystonic pain, central or primary pain and akathisia by Ford [11]. In studies on pain characteristics in PD, musculoskeletal pain was reported to be between 44-70%, dystonic pain was 19-40%, radicular-neuropathic pain was 11-20%, and central pain was 10-13% [9, 12]. Musculoskeletal pains are the form most frequently seen in PD, and are generally associated with parkinsonian rigidity. These are characterized by muscle and joint pains, osseous deformities, decreased mobility, and impaired posture, spinal pain, stiffness, and cramps, and findings increase with Parkinsonian rigidity and akinesia. [11, 13, 14]. In a study evaluating spinal pain, it was reported that neck pain was more common in PD than low back pain [15]. Dopaminergic therapies are effective in pain control, but the addition of physiotherapy and exercise

techniques and anti-inflammatory therapies increase the success of treatment [11]. In addition, in the event of insufficient response to these methods, various forms of complementary medicine targeting several symptoms, particularly pain, can also be used. Acupuncture therapy is defined as the insertion and manipulation of fine needles on specific body areas, known as acupuncture points, located in the meridians, according to ancient Eastern theories of medicine. This treatment method is thought to provide the flow of energy (chi) essential for a healthy life, to harmonize or balance blood circulation, and to provide effective treatment by regulating body homeostasis [16, 17]. This method was employed in ancient Chinese medicine and has also become popular today. It can be applied using acupressure, needling, moxibustion, involving the application of heat, and electrical stimulation based on the principle of applying pressure to certain acupuncture points to improve patient health. Acupuncture is applied to cutaneous and subcutaneous muscle tissue. Melzack reported a 71% similarity between acupuncture points and myofascial trigger points, and that all such trigger points could probably be Ah-Shi acupuncture points [18].

Clinical studies have investigated the effectiveness of acupuncture therapy on motor symptoms in PD. However, data concerning the effectiveness of this method in the treatment of non-motor symptoms, particularly PD-related pain, are very limited. The purpose of this study was to investigate the effectiveness of acupuncture therapy on the severity of chronic neck pain of musculoskeletal origin, disability, and quality of life in patients with PD.

Materials and methods

The research was planned as a prospective, randomized, controlled study. The research was

conducted in strict accordance with the principles of the Helsinki Declaration, and approval was granted by the Abant İzzet Baysal University Medical Faculty Clinical Research Ethical Committee (2021/61).

The participants invited to take part were informed verbally and in writing about the purpose and duration of the study, the therapeutic methods to be used, and potential adverse effects and problems that might be encountered during follow-up using a 'Volunteer Information Form' prepared beforehand and based on the study protocol. Written consent was obtained from all individuals who consented to take part by signing the 'Volunteer Information Form.'

Patients: Forty participants (16 women and 24 men) who presented to the Abant İzzet Baysal University Medical Faculty Physical Medicine and Rehabilitation Clinic, Turkey, between April and July 2021 and were diagnosed as having idiopathic PD were invited to take part in the study. In the study, musculoskeletal neck pain was preferred in terms of standardization of acupuncture treatments and exercise practices.

The inclusion criteria were a diagnosis of PD, presence of chronic neck pain of musculoskeletal origin persisting for at least 3 months, regression or control of pain with levodopa therapy, use of a fixed dosage of anti-Parkinson medication for at least 1 year, and age 50-75 years.

The exclusion criteria were receipt of acupuncture therapy in the previous 6 months, causes of localized neck pain not associated with PD, presence of moderate-advanced dementia or psychiatric disease capable of limiting examination, testing, or therapy, organic cerebral pathology, restricted cooperation, receipt of anticoagulant therapy,

presence of inflammatory-type neck pain, history of trauma or surgery to the cervical region, and presence of neoplasia.

Demographic and clinical characteristics such as age, sex, and body mass index were recorded. Detailed histories were taken, systemic, locomotor, and neurologic examinations were performed, and existing laboratory and radiologic tests were assessed. No modification was made to medical treatment aimed at PD throughout the study in any case.

The study CONSORT (Consolidated Standards of Reporting Trials) flow diagram is summarized in Fig. 1.

Assessment methods

Hoehn and Yahr Scale: This scale consists of five stages and is widely used in the classification of PD. It provides an objective evaluation of the progression of the disease, from stage 0 (no sign of disease) to stage 5 (confinement to bed or wheelchair). All participants were classified using the Hoehn and Yahr scale before treatment [19].

Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS): This extensive scale is widely used for the clinical evaluation of the severity of PD. It consists of four sections involving non-motor findings, motor problems, motor findings, and treatment complications [20]. Thirteen non-motor findings in the first section of the scale and including the non-motor problems section (0- no finding, or normal, 4- severe finding) were evaluated before and at the end of treatment. Non-motor experiences of daily living (Part-I) of the MDS-UPDRS scale were used in the study.

Visual Analog Scale (VAS): A visual analog scale (VAS) was used to measure the severity
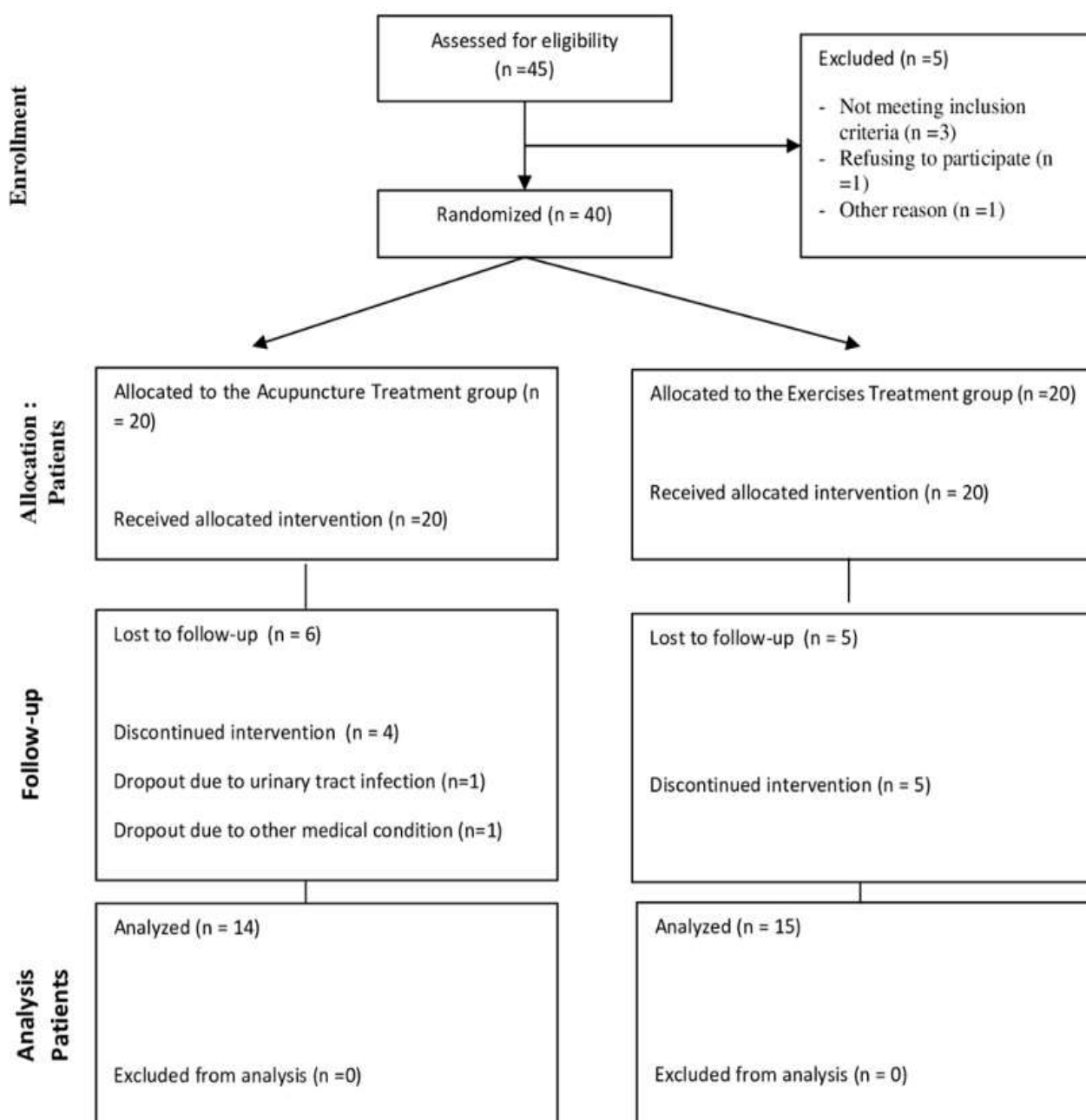
Figure 1. The study CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

of pain. Patients were asked to indicate the severity of their pain by marking the appropriate spot on a 10-cm line, with 0 indicating no pain and 10 the worst possible pain [21]. Patients were asked about the mean pain severity over the day before treatment and at the end of treatment.

Neck Disability Index (NDI): This index shows the extent to which neck pain affects the

patient's daily life activities. The scale consists of 10 questions including the parameters of pain severity, personal care, lifting, reading, headaches, work, concentration, driving, sleeping, and social activities. Each question is scored between 0 (no obstacle) and 5 (full obstacle). Total possible scores range between 0 (no disability) and 50 (complete disability). High scores indicate greater disability, and low scores low disability [22]. All participants

underwent NDI evaluation before and after treatment.

Health Assessment Questionnaire (HAQ):
This questionnaire consists of eight questions evaluating the effects of the individual's health status on daily life. Activities such as dressing, hygiene, eating, and walking are assessed. Higher scores indicate poorer health status [23]. All participants underwent HAQ evaluations before and after treatment.

Therapeutic Method: The participants were randomized into two groups, an acupuncture group (AG) and a control group (CG). Randomization was performed using a sequential list prepared using the random number generation function on Microsoft Excel© 2003 (Microsoft, Redmond, WA, USA) software. The first group (AG, n=20) was given a cervical exercise program in addition to acupuncture therapy, and the second group (CG, n=20) was started on the cervical exercises only.

Although no regular medical treatment was provided, patients were allowed to take paracetamol tablets if required, with a maximum daily dosage of 1 g. All participants were given pain diaries, in which they were asked to record their pain severities and paracetamol consumption at home.

Acupuncture Application
Treatment was administered by a single, experienced, acupuncture-certified physiatrist (Elif Yaksi) in all cases. Treatment was applied during the 'on' phase of the disease. All patients received a total of 10 sessions of acupuncture therapy, every two weeks. The GB 20, GB 21, GV 14, GV 20, LI 4, LI 10, ST 36, GB 34, SI 3, SI 9, SI 10, SI 11, and Ah-shi points, those most frequently used in chronic neck pain, were

selected [24] In addition, points related to treatment after acupuncture diagnosis were added to the treatment (Fig. 2).

A single needle was applied to the midline in a mean of six points at each session, with bilateral needling being applied to the other points. Single-use, nickel-tipped, sterile needles 0.25 * 25 mm or 0.25 * 40 mm in size (Hua Long, Kanze Co.Ltd, Turkey) were used during acupuncture, depending on the area involved. Needles were inserted to a depth of approximately 1.0-2.0 cm and were manipulated until de-qi was perceived by the patient (a feeling of numbness, prickling, distension, or pressure showing that the acupuncture needle has been inserted in the correct location). The needles were then left in place for approximately 30 min and then removed.

Before receipt of acupuncture therapy, patients were informed about the therapeutic technique and potential adverse effects, such as dizziness and somnolence, or pain, bleeding, or bruising occurring during the procedure.
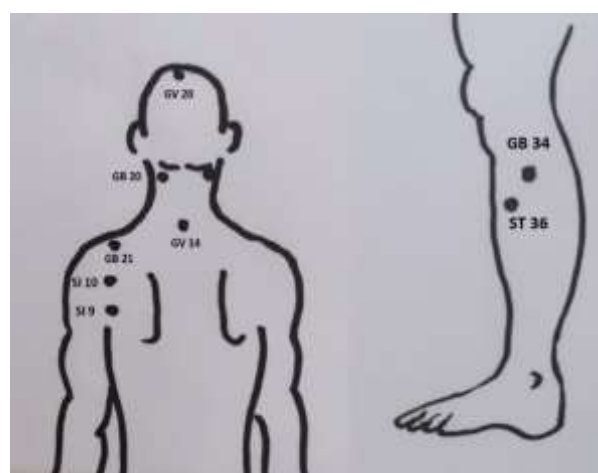

Figure 2. Commonly used acupuncture points for pain in Parkinson's disease.

Exercise Application
All patients were started on a home exercise program, consisting of cervical joint range of

motion exercises, cervical isometric strengthening exercises, and trapezius muscle strengthening exercises for five weeks, three sets a day, with at least 10 repetitions of each set. The exercises commenced approximately half an hour after the morning Parkinson's medication had been taken, when symptoms associated with PD such as rigidity, tremor, and bradykinesia, were less intense, when looser, faster, and more relaxed movements were possible, and when the patient felt subjective improvement.

Statistical Analysis

Analysis of the study data was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 21.0 software. Mean, standard deviation, median, maximum, and minimum values were calculated for all parameters. The normality of distribution between the two groups was first determined using the Shapiro-Wilk test. Non-parametric data was analyzed with using the Wilcoxon signed-ranks test to investigate within-group differences and paired sample t-test was used to compare intragroup changes of normally distributed variables. Two independent t-tests were used to compare the means between the groups for normally distributed data. The non-parametric Mann-Whitney U test was used to investigate potential between-group differences in non-parametric variables without normal distribution. The results were evaluated at a 95% confidence interval, and p values of <0.05 were considered statistically significant.

Table 1. Characteristics and demographic data in the patient groups.

Parameters	AG	CG	Total	*p*
Age				
Mean±SD	69.0±3.8	70.4±2.8	70.2±3.4	*0.22*
Min-Max	62.0/74.0	66.0/75.0	62.0/75.0	
Gender (%)				
Male	8 (57%)	9 (56%)	17 (59%)	*0.76*
Female	6 (43%)	6 (44%)	12 (41%)	
BMI				
Mean±SD	25.6±1.8	25.8±1.9	25.7±1.9	*0.95*
Min-Max	22.4-28.1	22.1-28.1	22.1-28.1	
Hoehn-Yahr Stage				
Median	2	2	2	*0.22*
Min-Max	1-4	1-4	1-4	
Duration of disease (years)				
Mean±SD	4.5±1.6	4.2±1.7	4.4±1.6	*0.62*
Min-Max	1-7	1-7	1-7	

AG: Acupuncture Group; CG: Control Group; BMI: Body Mass Index; SD: Standard deviation; Min: Minimum; Max: Maximum; α=0.05

Results

The 40 patients in the study were randomly assigned into two groups, AG (n=20) and CG (n=20). Eleven patients, six from AG and five from CG, were excluded from the study at the end of treatment due to failure to attend follow-ups, and the research was thus completed with 29 patients (AG n=14 and CG n=15). No adverse effects associated with exercise or acupuncture developed in the participating patients. Pain diaries were evaluated at the end of the study. No patient required any analgesic therapy.

The mean age of the patients in the study was 70.2±3.4 years. Twelve were women, and 17 were men. Musculoskeletal neck pain was present in all patients. No statistically significant difference was observed in the initial evaluations of patients' clinical characteristics and demographic data (p>0.05). The clinical characteristics and demographic data of the patients are summarized in Table 1. Patients' mean pre- and post-treatment VAS, NDI, MDS-UPDRS I, and HAQ values plus standard deviation are shown in Table 2.

Intragroup comparisons revealed a statistically significant decrease in VAS, NDI, MDS-UPDRS I, and HAQ values in both groups post-treatment compared with pre-treatment (p<0.05) (Table 2).

To compare VAS, NDI, MDS-UPDRS I, and HAQ values, statistical analysis was performed based on and pre- and post-treatment values for all parameters. Analyses revealed a significant difference in favor of the acupuncture group (p<0.05) (Table 2).

Table 2. A comparison of pre- and post-treatment values in and between the groups.

Parameters	AG (n:14)	CG (n:15)	*p*
VAS*			
Pre-treatment	6 (5-8)	8 (5-8)	
Post-treatment	1 (0-3)	4 (2-8)	*0.001[b]*
p	0.001 [a]	0.001 [a]	
NDI**			
Pre-treatment	29.0±3.5	27.7±3.9	
Post-treatment	9.1±6.1	23.8±6.1	*<0.001[d]*
p	<0.001 [c]	0.001 [c]	
MDS-UPDRS-I**			
Pre-treatment	20.7±5.4	20.2 ±7.2	
Post-treatment	17.9±5.1	18.7±7.1	*0.007[d]*
p	<0.001 [c]	<0.001 [c]	
HAQ**			
Pre-treatment	31.3±8.3	33.9 ±6.3	
Post-treatment	23.0±6.5	31.0 ±7.6	*<0.001[d]*
p	0.003 [c]	0.012 [c]	

*AG: Acupuncture Group; CG: Control Group; VAS: Visual Analog Scale, NDI: Neck Disability Index, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; HAQ: Health Assessment Questionnaire; SD: Standard deviation; Min: Minimum; Max: Maximum, *Median (Min-Max), ** Mean±SD (Min-Max), a: Wilcoxon Signed Ranks test, b: Mann-Whitney U test, c: Paired Sample T test, d: Independent Sample test.*

Discussion

The basic hypothesis in the present study was that acupuncture therapy applied in addition to cervical region exercises among individuals with musculoskeletal neck pain in PD could make an additional contribution to pain, functional status, and daily life activities. In light of that hypothesis, the effects of cervical exercises and the effectiveness of additional acupuncture therapy in PD were compared. The results showed statistically significant improvement after treatment in all measurement parameters compared with pre-treatment values. Intergroup analysis also showed that acupuncture therapy provided significant improvement in pain control and also functional improvement compared with the control group.

The accumulation of credible evidence regarding acupuncture therapy, which has been widely used for thousands of years in Asian societies due to its therapeutic effect, has led to its worldwide adoption as a complementary therapy. Acupuncture treatment is accepted as a reliable treatment method in PD for many years and has a low adverse effect profile. In this method, although needles are inserted at localized points, positive effects are obtained in terms of acupuncture effectiveness both in terms of local and general body regulation [25]. Acupuncture therapy has become widely used in recent years in the treatment of several painful conditions, particularly musculoskeletal pains and migraine [26]. Acupuncture is thought to produce an increase in the release of endogenous opioids in the pain control mechanism, to alter spinal signal transmission by activating the afferent nerves, and thus to induce signals that modulate pain perception in the brain by causing pre- and post-synaptic inhibition of pain transmission [27]. Increasing evidence-based data and evaluation of the

effectiveness of the therapy using objective measurement methods such as functional magnetic resonance imaging (fMRI) are yielding growing objective evidence regarding the effectiveness of acupuncture. Lan et al. performed acupuncture on patients with migraine and evaluated the outcomes using fMRI. The central pain pathways affected in the group receiving acupuncture were found to differ from the pathways affected in the placebo group [28].

Treatment strategies in PD aim to protect dopaminergic neurons by obtaining neuroprotective effects. The main goals of using acupuncture therapy in PD are to achieve neuroprotective effects, and, in addition to this, provide symptomatic relief [29]. Various studies are showing that acupuncture provides neuroprotection. Park et al. produced neuronal cell loss induced in the nigrostriatal dopaminergic system with 6-hydroxydopamine in rat models. It has been reported that acupuncture provides neuroprotective effects [30]. In another study, they performed acupuncture after creating a PD model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MTPT) in mouse models. As a result of the study, they reported that the use of acupuncture provided neuroprotective effects on the substantia nigra and striatum. They also reported that it reduced microglial activation and inflammation [31]. In another study, it was shown that long-term high-frequency electro-acupuncture treatment performed on rat models with induced PD prevented neuronal loss in the substantia nigra and ventral tegmental area, and increased brain-derived neurotrophic factor (BDNF) mRNA levels [32]. Similar to this study, it has been reported that electroacupuncture at different frequencies applied to the GB34 point in mouse models has a protective effect on tyrosine

hydroxylase positive dopaminergic neurons and the expression of some proteins that have a protective effect on these neurons [33]. Although neck pain is encountered as a non-motor symptom in PD, an increase in pain intensity can be observed with the increase in motor findings. In this study, in addition to the analgesic effects of acupuncture, its effect on motor symptoms may have contributed additionally to pain control.

Although the pathophysiology of pain in PD is not clearly understood, it is thought that supraspinal mechanisms may play a role. One study evaluated patients with PD with and without persistent pain using fMRI. The authors found structural changes in the supraspinal area of patients with persistent pain. They also reported that there was a conduction disorder in the areas of the accumbens and hippocampus [34]. Chen et al. evaluated the pain response in PD-induced rats with fMRI. Ordinarily, a decrease in cerebral blood flow is detected in the striatum after painful stimuli. However, they determined that the weakened cerebral blood flow decrease in the lesioned striatum on nociceptive stimuli in rats with PD [35]. Yu et al.'s study involved 16 patients with PD-related pain, six of whom were started on non-steroidal anti-inflammatory drugs (NSAIDs), whereas the other nine received acupuncture in addition to NSAIDs. Although statistically significant improvement was determined in total UPDRS scores in the acupuncture group, no significant change was determined in UPDRS subscale scores or VAS values. fMRI evaluation was also performed in that study, and acupuncture therapy was reported to modulate regions of the brain associated with sensory-discriminative and emotional areas [36]. In addition to evidence-based objective data, several studies have also reported that the analgesic effects of acupuncture differ from those of sham acupuncture. Vas et al. compared the efficacy of acupuncture and placebo transcutaneous electrical nerve stimulation (TENS) in patients with neck pain. The authors reported that the improvement in quality of life, increase in neck mobility, and decrease in analgesic use were significantly greater in the group receiving acupuncture compared with the placebo group [37]. Similarly, Liang et al. compared acupuncture and sham acupuncture in patients with chronic neck pain, reporting significant improvement in pain and general health in the treatment group compared with the sham group [38]. Similar to these patients, significant improvement was achieved in terms of pain and quality of life in the acupuncture group compared with the group that did not receive acupuncture. However, in contrast to those studies, a control group was employed instead of a sham group in our research. There have been systematic reviews reporting that acupuncture is superior to sham applications in patients with neck pain. One such systematic review reported a moderate level of evidence indicating that acupuncture achieved more effective pain control in patients with neck pain at the end of treatment and in short-term evaluations compared with sham acupuncture. That review also stated that patients receiving acupuncture reported less pain and disability in the short term [39]. Another systematic review also reported a moderate level of evidence that acupuncture therapy was more effective than sham acupuncture in patients with chronic neck pain [40]. We therefore concluded that our use of a control group, rather than a sham group, would not affect the results.

Studies concerning PD have particularly evaluated the effects of acupuncture on motor findings. One meta-analysis reported a more marked increase in motor performance in patients with PD following acupuncture therapy

on the UPDRS and Webster scales [41]. This suggests that in addition to the effects of acupuncture on the pain pathway, it may also make an additional contribution to pain treatment by producing improvement in motor functions, decreased rigidity, and improvement in posture. We think that improvement in motor findings may have contributed to healing, although UPDRS scores were not evaluated. Significant improvement was achieved in non-motor findings on the UPDRS (such as sleep disorders, depression, and anxiety). Fu et al. reported that a depressive mood state and sleep disorders were independent predictors of pain in PD [42]. Evidence that acupuncture exhibits positive effects on sleep patterns and psychiatric symptoms in patients with PD shows that acupuncture therapy may have provided analgesia through its effects on pain and its effects on different non-motor findings [41]. In contrast to dry needling therapy, traditional acupuncture is performed at local and distant points. This shows that acupuncture may be effective through systemic mechanisms in addition to local effects [43]. Irnich et al. evaluated the efficacy of acupuncture, sham acupuncture, and dry needling therapy in patients with chronic neck pain. The authors reported that acupuncture was superior to sham acupuncture in terms of movement-related pain, and that acupuncture applied to a distant region resulted in a greater improvement in joint range of motion than dry needling. That study attributed the superiority of non-segmental acupuncture to local dry needling to activation of descending inhibitory pain control systems, rather than to stimulation of the endogenous opioid system [44]. In addition to the analgesic effects of acupuncture in the present study, it may also have contributed to improvement through systemic effects, particularly on motor functions.

The principal limitations of this study are the small sample size and the fact that patients were in different clinical stages (Hoehn Yahr 1-4). Other limitations include the absence of a sham group and the fact that parameters such as motor functions, sleep, and mood, potentially related to pain, were not evaluated using a specific method. A further limitation is that long-term post-treatment outcomes were not evaluated.

Conclusion
In addition to impairment of the pain pathways, factors such as motor function compromise and sleep and mood disorders also contribute to the development of pain in PD. Due to its local and systemic effects, acupuncture therapy is, therefore, a safe method capable of use in the treatment of pain. Further, more extensive, randomized, placebo-controlled studies are now needed to evaluate the effectiveness of treatment.

Conflict of Interest: The authors declare that they have no conflict of interest.
Ethical statement: Bolu Abant İzzet Baysal University ethics committee approved the study protocol (Approval ID: 2021/61).

Open Access Statement

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