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CLINICAL TRIAL REPORT

Fire Needling Therapy versus Usual Care for Parkinson's Disease-Related Chronic Pain: A Pilot Randomized Controlled Trial

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Introduction: Parkinson's disease (PD)-related chronic pain is a prevalent non-motor symptom, this study aimed to detect the effect and safety of fire needling therapy (FNT) for PD-related chronic pain relief.

Methods: Patients with PD-related chronic pain were randomly allocated to FNT group and control group with a treatment phase of 8 weeks and a follow-up phase of 4 weeks. Primary outcome was the King's Parkinson's Pain Scale (KPPS), Secondary outcomes included Visual Analogue Scale (VAS), Unified Parkinson's Disease Rating Scale-III (UPDRS-III), and the Parkinson's Disease Questionnaire-39 (PDQ-39). Study was registered on Chinese Clinical Trial Registry (Registered number: ChiCTR2400084951).

Results: 60 participants were randomized, with 30 in the FNT group and 30 in the control group. KPPS was significantly influenced by the interaction of treatment and time, with a significant reduction in pain observed in the FNT group compared to the control group at Week 4 (difference [95% CI]: −20.693[−27.619,-13.767], P<0.001), Week 8 (difference [95% CI]: 44.680[−52.359,-37.000], P<0.001), and Week 12 (difference [95% CI]: −44.982[−52.771,-37.193], P<0.001). For VAS, UPDRS-III, and PDQ-39, there were significant differences between groups at Week 4, Week 8, and Week 12.

Conclusion: FNT could be an effective and safe method for managing PD-related chronic pain. However, large-sample studies conducted in multiple centers are necessary to further verify the findings in the future.

Keywords: parkinson's disease, pain, fire needling therapy, acupuncture, pilot randomized controlled trial

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by a range of motor symptoms.[1,2] However, non-motor symptoms such as depression, sleep disturbances, visual dysfunction, cognitive impairment, and pain are also highly prevalent in patients with PD, yet they are often under-reported and poorly treated.[3] These non-motor symptoms substantially affect patients' quality of life.

In 2021, the age-standardized incidence rate of PD in China was 24.3 per 100,000, considerably higher than the global average of 15.6 per 100,000. PD-related pain affects 20% of patients at the time of diagnosis, associated with the early motor stage.[4] In the intermediate stages, chronic pain is present in 60% of patients.[5] Throughout the disease course, the prevalence of PD-related pain has been reported to be as high as 80%.[6] However, pain in PD is a complex issue that is often not well understood by clinicians, resulting in limited awareness of PD-related pain. Despite being more frequent and intense than other types of pain in the general population, PD-related pain is largely undertreated.[7,8] Typically, this pain is managed by adjusting strategy of dopaminergic treatment, which may not address the underlying causes effectively.

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The Chinese guideline[9] mentions opioid analgesics for treating PD-related pain, however, some side effects of opioids, such as constipation, overlap with PD symptoms.[10] Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for relieving pain, but long-term use may increase the risk of gastrointestinal and cardiovascular diseases.[11] Therefore, alternative options are needed for patients with PD experiencing pain. Acupuncture is an effective therapy for managing various types of pain, with rigorous evidence confirming its efficacy and slight side effects.[12–15] The commonly used acupuncture points include GV16 (Fengfu), GB20 (Fengchi), UB10 (Tianzhu), and GB12 (Wangu), which can alleviate the motor symptoms of PD as well as improve the non-motor symptoms. Fire needling therapy (FNT) is one of the most common forms of acupuncture, with a history dating back thousands of years. A red-hot needle is inserted into the acupuncture points, eliciting a stronger response from the human body with additional heat stimulus, thereby achieving a better therapeutic effect.

However, studies on FNT for PD-related pain are still lacking, thus, we aimed to conduct a pilot randomized controlled trial (RCT) to detect the effect and safety of FNT for PD-related chronic pain relief.

Methods

Study Design and Setting

This single-center, two-arm pilot randomized controlled trial (RCT) was conducted at Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University according to the Declaration of Helsinki. The intervention included 8 weeks of intervention and 4 weeks of follow-up (Figure S1). This study was approved by the research ethic committee (No. 2021BL02-100-02) of the above hospital and registered on Chinese Clinical Trial Registry (Registered number: ChiCTR2400084951). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guideline for the designing and reporting of this trial.

Participants

Participants were recruited from the outpatient units of acupuncture and moxibustion department from January 2022 and ended in February 2023.

Diagnosis Criteria

Participants were diagnosed with chronic pain related to PD if they met the following criteria.

1. Diagnosed idiopathic PD with "Diagnostic criteria for Parkinson's disease in China (2016 edition)[16]";
2. Pain lasted at least 3 months;
3. Determined the relation between PD and chronic pain by the concurrent onset or exacerbation of pain with motor symptoms, the alleviation of pain through dopaminergic medications, the intensification of pain during the Off phase, and/or the manifestation of pain during choreiform dyskinesia;
4. Excluded other factors that cause pain.

Inclusion Criteria

1. Aged 50–80 years, male or female.
2. Diagnosed with PD-related chronic pain based on the abovementioned diagnosis criteria.
3. Modified Hoehn and Yahr stage ≤ III.
4. Anti-PD medications were stably used for at least 4 weeks before randomization, and adjustments of pharmacotherapy during the trial were permitted if deemed clinically necessary.
5. Written informed consent.

Exclusion Criteria

1. Regular use of opioid-containing drugs within 6 months.
2. Drug or alcohol abuse.
3. Had acupuncture therapy within 3 months.

4. Had serious acute or chronic organic or mental disorders (Mini Mental State Examination score ≤ 24).
5. Pregnant or breastfeeding women.
6. Coagulation diseases (such as hemophilia).
7. Had participated in other clinical trials within 3 months.
8. Cardiac pacemaker, metal allergy or fire needle phobia.

Randomization and Allocation Concealment

Eligible participants were randomly allocated to the FNT group and control group in a ratio of 1:1. The randomization sequence was generated using R software (version 4.1.3). This sequence was placed in opaque envelopes, each marked with an enrollment number on the cover. All processes were conducted by an independent statistician who did not participate in the subsequent implementation or statistical analysis. Researchers were instructed to open the envelopes in the order of patient enrollment and to implement the intervention based on the group information contained within the envelopes.

Blinding

Due to the nature of the intervention, the participants and acupuncturists in our study were not blinded. However, data analysts and outcome assessors were blinded to group assignments.

Interventions

Control Group (Usual Care)

Participants in control group used individualized optimal drug therapy according to the "Chinese guidelines for the treatment of Parkinson's disease (fourth edition)".[9] Anti-PD medications were adjusted and stabilized at least 4 weeks before randomization, and participants took the medications regularly during the study. Any adjustment of medications during the study was permitted if deemed clinically necessary.

FNT Group (Fire Needling Therapy)

Participants in FNT group received both usual care (same as the control group) and FNT.

FNT was semi-standardized based on traditional Chinese medicine theory, with the prescription developed through a literature review[17] and clinical practice. The acupuncturists were required to have a Chinese medicine practitioner license and at least five years of experience. Each participant received FNT from one acupuncturist throughout the trial. The acupuncture points included bilateral GV16 (Fengfu), GB20 (Fengchi), UB10 (Tianzhu), GB12 (Wangu), and the ashi point (sensitive point where patients feel pain) (Table S1, Figure S2).

FNT was performed using sterile disposable needles (Hwato Needles, Sino-foreign Joint Venture Suzhou Hwato Medical Instruments, China, size 0.40mm x 40mm). The needles, heated until red-hot over a spirit lamp, were inserted to a depth of 3 mm to 5 mm at the acupuncture points and swiftly withdrawn without retention. Each selected point was pricked twice. After insertion, the needle hole was pressed with a sterilized dry cotton ball for 30 seconds. Participants received FNT 3 times per week (ideally on Monday, Wednesday, and Friday) for 8 weeks.

Rescue Treatment

Participants were allowed to use gabapentin capsules (0.1g/T, Jiangsu Nhwa Pharmaceutical Co., Ltd., Jiangsu, China) and ibuprofen sustained-release capsules (0.3g/T, Tianjin Smith Kline & French Laboratories Ltd., Tianjin, China) as rescue medications.[9] The details of their usage were recorded in the case report form (CRF).

Outcomes

Primary Outcome Measurement

The King's Parkinson's Pain Scale (KPPS) was used to assess changes in pain from baseline. KPPS has 7 domains including 14 items that measure musculoskeletal, chronic, fluctuating, nocturnal, orofacial, edematous, and radicular pain. Each item is scored based on severity (0, none to 3, very severe) multiplied by frequency (0, never to 4, all the time), resulting in a subscore ranging from 0 to 12. The total score is the sum of all subscores, and higher scores indicate worse pain.[18,19] KPPS was assessed at baseline, Week 4, Week 8, and Week 12.

Secondary Outcome Measurement

Pain intensity: Visual Analogue Scale (VAS) was used to assess the pain intensity. VAS is an 11-point self-administrated tool, ranging from 0 (no pain at all) to 10 (worst pain).[20] VAS was assessed at baseline, Week 4, Week 8, and Week 12.

Motor function: Unified Parkinson's Disease Rating Scale-III (UPDRS-III) was used to assess the motor function. The UPDRS is a tool to measure the severity and progression of PD and consists of 6 domains, the third domain is motor function assessment. The motor domain has 14 items, each scored on a 0–4 rating scale, higher scores indicate increased severity.[21,22] UPDRS-III was assessed at baseline, Week 4, Week 8, and Week 12.

Quality of life: The Parkinson's Disease Questionnaire-39 (PDQ-39) was used to assess the quality of life of participants with PD. PDQ-39 has 39 questions across 8 domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communications, and bodily discomfort. Each item is scored on a 0–4 rating scale, with higher scores indicating a worse quality of life.[23,24] PDQ-39 was assessed at baseline, Week 4, Week 8, and Week 12.

Compliance was assessed at Week 8, with participants scoring below 80% considered to have poor compliance. $Compliance\ score\% = \frac{\text{Acutual treatment sessions}}{\text{Required treatment sessions}} \times 100\%$

Adverse Events

Adverse events (AEs) were investigated and recorded weekly by researchers. Serious adverse events were reported and managed based on regulations. Common adverse events associated with FNT include dizziness, subcutaneous hematoma, infection, etc. Common adverse events related to anti-PD medications include nausea, constipation, emesis, edema, hypotension, fatigue, etc.

Sample Size Calculations

No previous studies have examined the KPPS concerning FNT, while one study indicated that a reasonable minimum number of participants from the population of interest is 30.[25,26] Therefore, a total of 60 participants were required in our study.

Statistical Analysis

All data were assessed using R software (version 4.3.2). All data were validated for normal distribution using the Shapiro–Wilk test before subsequent statistical analyses. Continuous data were described using the mean (standard deviation) or median (interquartile range), depending on the normality of the distribution. Categorical data were described using numbers and percentages. KPPS, VAS, UPDRS-III, and PDQ-39 were analyzed using a mixed-effects model based on repeated measurements. Compliance and adverse events were analyzed using the chi-squared test. A two-tailed p-value<0.05 was considered statistically significant. All test indicators were analyzed using the Intention-To-Treat (ITT) approach, with missing data obtained using the multiple imputation method. Per-protocol (PP) analysis was conducted as a sensitivity analysis.

Results

Participant Characteristics

We screened a total of 103 participants, of whom 43 were excluded after screening. 60 participants were randomized, with 30 in the FNT group and 30 in the control group. All 60 participants were included in the ITT analysis and safety analysis. Among these, 28 participants (two dropouts due to deep brain stimulation surgery) in the FNT group and 29 participants (one dropout due to loss of contact) in the control group completed all treatments by Week 8 (Figure 1).

There was no significant difference in baseline characteristics, all data were distributed normally. The mean (SD) age was 64 (5.73) years, and 28 (46.67%) participants were female. Most participants (53 [88.33%]) were at levels 1.5–2.5 of the Modified Hoehn and Yahr stage. The mean (SD) KPPS score was 69.65 (10.76) (Table 1).

Primary Outcome

KPPS was significantly influenced by the interaction of treatment and time, with a significant reduction in pain observed in the FNT group compared to the control group at Week 4 (difference [95% CI]: −20.693[−27.619,-13.767], P<0.001),

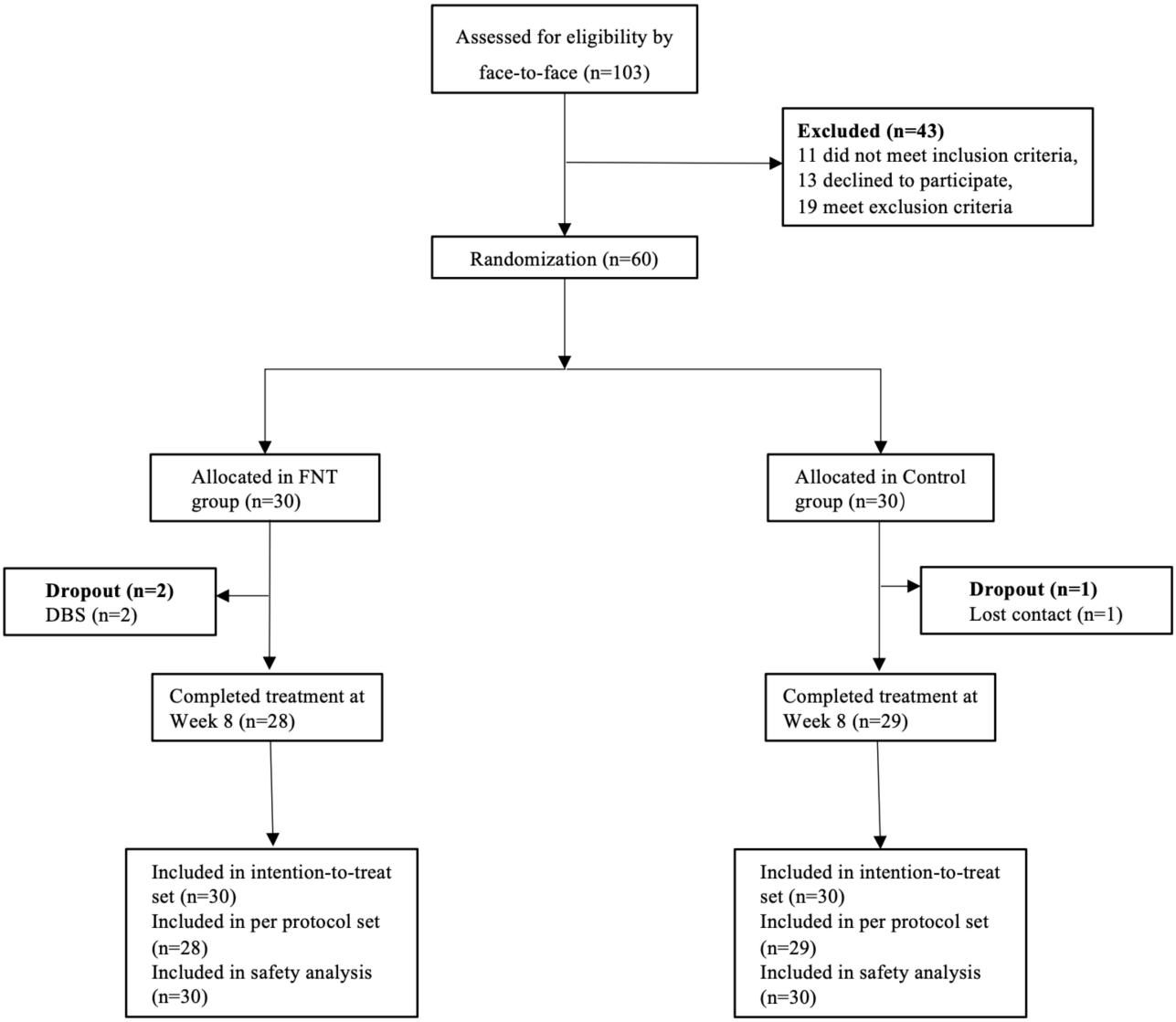

Figure 1 Trial flow chart.
Abbreviations: DBS, Deep Brain Stimulation; FNT, Fire Needling Therapy.

Week 8 (difference [95% CI]: 44.680[−52.359,-37.000], P<0.001), and Week 12 (difference [95% CI]: −44.982 [−52.771,-37.193], P<0.001) (Table 2, Figure 2).

Secondary outcomes

The VAS, UPDRS-III, and PDQ-39 scores were significantly influenced by the interaction of treatment and time. Significant improvements in VAS scores were observed in the FNT group compared to the control group at Week 4 (difference [95% CI]: −3.071[−3.906,-2.236], P<0.001), Week 8 (difference [95% CI]: −4.840[−5.799,-3.882], P<0.001), and Week 12 (difference [95% CI]: −4.971[−5.727,-4.215], P<0.001). Similarly, there was a statistically significant improvement in UPDRS-III scores in the FNT group compared to the control group at Week 4 (difference [95% CI]: −9.330[−12.674,-5.986], P<0.001), Week 8 (difference [95% CI]: −14.169[−17.316,-11.022], P<0.001), and Week 12 (difference [95% CI]: −13.103[−16.111,-10.096], P<0.001). The PDQ-39 scores also indicated that the FNT group had a significantly better quality of life compared to the control group at Week 4 (difference [95% CI]: −11.164[−19.828,-2.500], P<0.001), Week 8 (difference [95% CI]: −19.010 [−27.104,-10.915], P<0.001), and Week 12 (difference [95% CI]: −19.491[−27.743,-11.239], P<0.001) (Table 2, Figure 2).

Table 1 Characteristics of the Patients at Baseline

Characteristics	All (N = 60)	FNT group (N = 30)	Control group (N = 30)
Sex, n (%)			
Male	32 (53.33%)	18 (60.00%)	14 (46.67%)
Female	28 (46.67%)	12 (40.00%)	16 (53.33%)
Age, Mean (SD)	64.43 (8.33)	62.17 (8.19)	66.70 (7.98)
Hoehn-Yahr stage, n (%)			
1	3 (5.00%)	1 (3.33%)	2 (6.67%)
1.5	19 (31.67%)	11 (36.67%)	8 (26.67%)
2	16 (26.67%)	10 (33.33%)	6 (20.00%)
2.5	18 (30.00%)	5 (16.67%)	13 (43.33%)
3	4 (6.67%)	3 (10.00%)	1 (3.33%)
KPPS, Mean (SD)	69.65 (10.76)	69.73 (9.12)	69.57 (12.34)
VAS, Mean (SD)	6.83 (1.342)	6.83(1.262)	6.83(1.440)
UPDRS-III, Mean (SD)	37.82 (5.789)	37.67(5.274)	37.97(6.349)
PDQ-39, Mean (SD)	72.50 (15.91)	71.60 (14.74)	73.40 (17.21)

Abbreviations: FNT: Fire Needling Therapy, KPPS: The King's Parkinson's Pain Scale, PDQ: The Parkinson's Disease Questionnaire, SD: Standard Deviation, UPDRS: Unified Parkinson's Disease Rating Scale, VAS: Visual Analogue Scale.

Table 2 Primary and Secondary outcomes

	FNT group (N = 30)	Control group (N = 30)	FNT group vs Control group	
Primary outcome			**Difference(95% CI)**	**P***
KPPS, mean(SD)				
Baseline	69.73(9.120)	69.57(12.342)	−0.615(−6.451,5.221)	0.834
Week4	48.88(13.722)	68.05(12.357)	−20.693(−27.619,-13.767)	<0.001
Week8	22.97(15.236)	67.24(13.037)	−44.680(−52.359,-37.000)	<0.001
Week12	23.90(15.139)	68.34(13.609)	−44.982(−52.771,-37.193)	<0.001
Secondary outcome			**Difference(95% CI)**	**P***
VAS,mean(SD)				
Baseline	6.83(1.262)	6.83(1.440)	−0.065(−0.797,0.666)	0.859
Week4	4.01(1.692)	6.85(1.494)	−3.071(−3.906,-2.236)	<0.001
Week8	1.93(1.872)	6.68(1.673)	−4.840(−5.799,-3.882)	<0.001
Week12	2.25(1.459)	7.12(1.351)	−4.971(−5.727,-4.215)	<0.001
UPDRS-III, mean(SD)				
Baseline	37.67(5.274)	37.97(6.349)	−0.233(−3.397,2.932)	0.884
Week4	28.53(6.387)	37.40(6.050)	−9.330(−12.674,-5.986)	<0.001
Week8	23.52(5.348)	37.18(6.355)	−14.169(−17.316,-11.022)	<0.001
Week12	25.25(5.199)	37.89(5.988)	−13.103(−16.111,-10.096)	<0.001
PDQ-39, mean(SD)				
Baseline	71.60(14.738)	73.40(17.206)	−1.779(−10.467,6.909)	0.683
Week4	60.94(14.552)	71.74(17.307)	−11.164(−19.828,-2.500)	0.012
Week8	51.30(13.667)	70.02(16.102)	−19.010(−27.104,-10.915)	<0.001
Week12	51.84(14.064)	70.78(16.345)	−19.491(−27.743,-11.239)	<0.001

Notes: *KPPS, VAS, UPDRS-III, and PDQ-39 were significantly influenced by the interaction of treatment and time. Thus, the P value at each time-point was presented. P was analyzed using a mixed-effects model based on repeated measurements.

Abbreviations: FNT, Fire Needling Therapy; KPPS, The King's Parkinson's Pain Scale; PDQ, The Parkinson's Disease Questionnaire; SD, Standard Deviation; UPDRS, Unified Parkinson's Disease Rating Scale; VAS, Visual Analogue Scale.

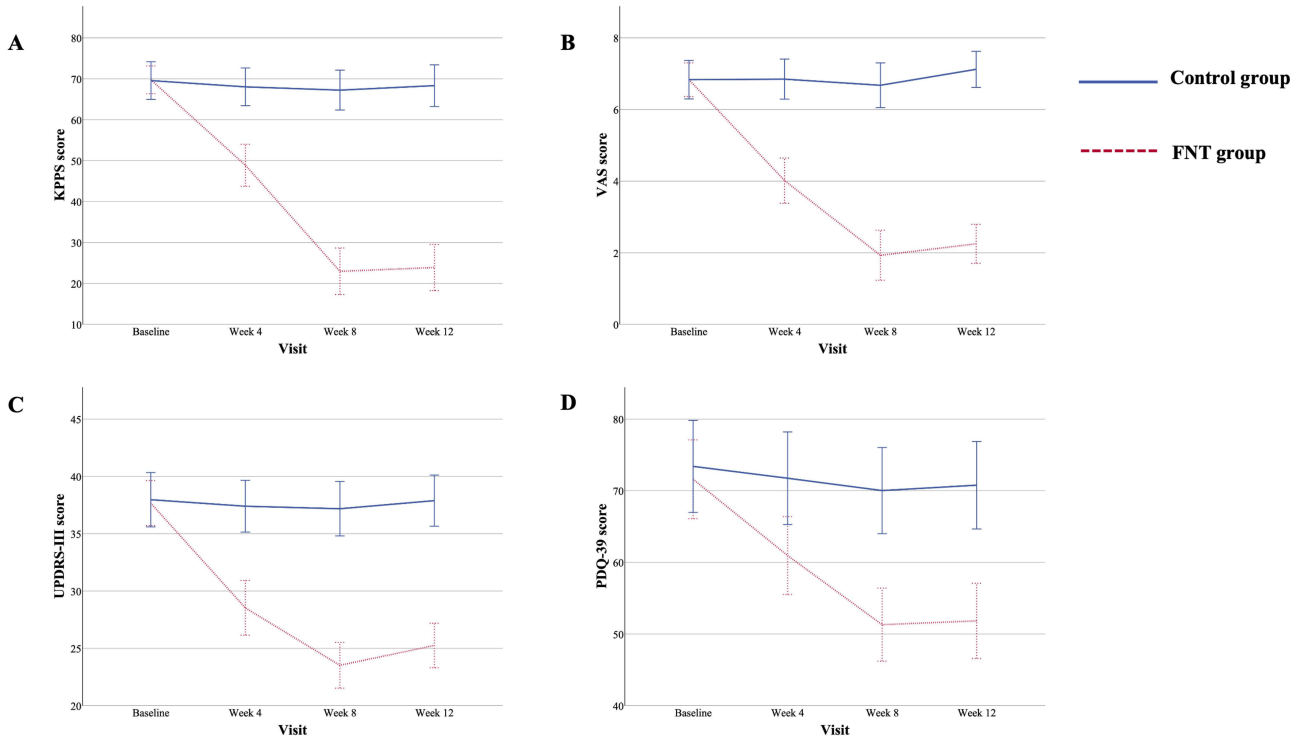

Figure 2 Therapeutic effects of FNT. (**A**) Changes of KPPS score, (**B**) Changes of VAS score, (**C**) Changes of UPDRS-III score, (**D**) Changes of PDQ-39 score.
Abbreviations: FNT: Fire Needling Therapy, KPPS: The King's Parkinson's Pain Scale, PDQ: The Parkinson's Disease Questionnaire, UPDRS: Unified Parkinson's Disease Rating Scale, VAS: Visual Analogue Scale.

The compliance of participants in each group was ≥80%, which was considered good compliance. Both groups demonstrated good compliance, with 93.33% in the FNT group and 96.67% in the control group (Table 3). The results of the sensitivity analysis using PP analysis were similar to those of the ITT analysis (Tables S2 and S3).

Safety

No severe adverse events were observed in either group. A total of 15 adverse events occurred in our study (Table 3). Anti-PD medication-related adverse events included: 5 participants experienced nausea, 2 participants had lower limb

Table 3 Compliance Data, Safety Assessment

Compliance		**FNT group (N=30)**	**Control group (N=30)**	**P***
Participants received at least 20-session treatment (24 sessions in total, compliance rates ≥ 80%)		28	29	1.000
Compliance data, No.(%)	*Low*	2(6.67%)	1(3.33%)	
	High	28(93.33%)	29(96.67%)	
Safety assessment, No.(%)				
Total adverse events		6	9	0.147
Anti-PD medication related	*Nausea*	1(16.67%)	4(44.44%)	
	Lower limbs edema	1(16. 67%)	1(11.11%)	
	Orthostatic hypotension	0(00.00%)	2(22.22%)	
	Palpitation	1(16. 67%)	2(22.22%)	
FNT related	*Subcutaneous hematoma*	3(50.00%)	0(0.00%)	

Note: Adverse events were analyzed in participants who received treatment at least once. *Analyzed using chi-squared test.
Abbrevition: FNT: Fire Needling Therapy.

edema, 2 participants had orthostatic hypotension, and 3 participants had palpitations. FNT-related adverse events included: 3 participants had subcutaneous hematomas. All participants healed completely within one week. There was no significant difference between the two groups. Two patients in FNT group and three patients in control group took the rescue medicine.

Discussion

In our study, participants in FNT group showed greater improvement in pain compared to the control group. Additionally, patients with PD who received FNT exhibited better enhancements in motor function and quality of life. These effects persisted for at least 4 weeks post-treatment. No severe adverse events were found in either group, but participants in control group experienced more anti-PD medication-related adverse events. These results indicate that FNT may be an effective and safe method for alleviating pain in patients with PD. Interestingly, during the trial, participants in the FNT group reported improvements in constipation and restless legs. Moreover, they noted a reduced onset time for anti-PD medications (Pramipexole Hydrochloride Tablets and Levodopa and Benserazide Hydrochloride Tablets) and a prolonged duration of the medication's therapeutic effects.

To the best of our knowledge, no studies have specifically investigated the effects of FNT on PD-related pain. We found merely one study[12] demonstrating that manual acupuncture could alleviate PD-related pain by modulating brain regions associated with both sensory-discriminative and emotional aspects, which is consistent with our findings. This study, however, had a small sample size of only 16 participants and did not explore the effects of acupuncture on motor function and quality of life. Whereas Jiang et al[27] suggested that manual acupuncture tended to improve hypometric gait and restructure the activation of the cerebral cortex, which could be a potential mechanism explaining the improved motor function observed in our study. Furthermore, Fan et al[28] found that manual acupuncture could relieve anxiety in patients with PD, which aligns with our study's results showing significantly better PDQ-39 scores in the FNT group compared to the control group. Besides, the improvement in constipation reported by participants in our study is supported by another study,[29] which introduced that acupuncture effectively alleviated constipation symptoms, with the treatment effect lasting up to 4 weeks.

Other non-pharmacological therapies, we found that transcranial direct current stimulation[30] and transcranial magnetic stimulation,[31] have shown effects in improving PD-related pain. In our study, the primary acupuncture points were located around the cranial base, which can effectively stimulate the blood supply to brain,[32] thereby triggering brain function and potentially contributing to pain relief and improved motor and other non-motor symptoms.

Needling at acupuncture points stimulates peripheral nerves, causing the release of endogenous opioids, such as endorphins and enkephalins, in the central nervous system, which reduces pain perception by inhibiting pain transmission along the spinal cord to the brain. Moreover, acupuncture may enhance the production of neurotransmitters such as serotonin and norepinephrine, which are involved in modulating pain and improving motor function.[33] Acupuncture also appears to reduce neuroinflammation by decreasing pro-inflammatory cytokines and promoting neuroprotective factors, thus potentially alleviating PD-related pain.[34,35]

Based on traditional Chinese medicine theory, the imbalance between "Yin" and "Yang" is the major etiological factor of PD, and under modern lifestyles, the "Yang deficiency" is frequently observed among patients with PD. Herbal medicine and acupuncture are effective in regulating "Yin" and "Yang", while herbal medicine carries a risk of hepatotoxicity.[36] FNT, a specialized form of acupuncture, provides stronger stimulation with extra heat, thus, FNT can effectively augment "Yang" in patients with PD, eventually relieving the overall symptoms without significant side effects.

Our study has several limitations. First, we did not use a sham control, which is not always the optimal control in different studies. Our study aimed to detect the effect and safety of FNT for PD-related pain relief, which has been demonstrated. Secondly, only Chinese participants were included in this study, potentially introducing a placebo effect influenced by cultural factors. To address this, future research should consider multicenter studies to mitigate the impact of cultural differences. Thirdly, the participants and acupuncturists were not blinded in our study, making it difficult to exclude placebo effects. Finally, the sample size in our study was relatively small, limiting the generalizability of our results. However, this is a pilot study that provides insights and directions for future research.

Conclusion

Based on our current results, compared with control group (anti-PD medications), FNT had better effects in alleviating pain, as well as improving motor function and quality of life. Thus, FNT could be an effective and safe method for managing PD-related chronic pain. However, large-sample studies conducted in multiple centers are necessary to further verify the findings in the future.

Data Sharing Statement

All the data used in this study can be assessed from the corresponding author (Peng Chen) with appropriate reasons.

Ethics Approval and Consent to Participate

This study was approved by the research ethic committee (No. 2021BL02-100-02) of the above hospital and registered on Chinese Clinical Trial Registry (Registered number: ChiCTR2400084951). All participants provided written informed consent.

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Disclosure

The authors declare that they have no competing interests in this work.

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