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Original Research

Acute Effect of Transcutaneous Auricular Vagus Nerve Stimulation on Hand Tremor in Parkinson's Disease: A Pilot Study of Case Series

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Abstract

Objectives: The aim of this study is to investigate the effects of non-invasive vagus nerve stimulation (VNS) on tremor in Parkinson's disease (PD).

Methods: This single-center, prospective, and implementation study with before-after design included five participants diagnosed with PD. Auricular VNS was applied to each participant 3 times on different days. VNS was applied to the participants as the right ear, left ear, and bilateral ear. The cardiovascular parameters of the participants were evaluated with Kubios HRV Standard and tremor with UPDRS tremor subscale and smartphone application before and after the intervention.

Results: Significant decrease in diastolic blood pressure (p=0.043) was found in participants who underwent bilateral auricular VNS. Although there was no significant change in the UPDRS tremor subscale, decreases in the maximum tremor amplitude in the x (p=0.043) and y (0.014) planes were detected in the measurements made with the smartphone application.

Conclusion: In this study, a decrease in the tremor amplitude measured in the 3D plane with auricular VNS was found in patients with PD.

Keywords: Parkinson's disease, tremor, vagus nerve stimulation

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Parkinsonism clinical syndrome is based on the presence of basic clinical motor features such as resting tremor, rigidity, bradykinesia, and postural instability. Parkinsonism is the observation of these clinical features in different combinations, and in most patients, the etiologic factor cannot be identified. Idiopathic Parkinson's disease (PD) is the most common cause of this syndrome and is the most common movement disorder after essential tremor.[1,2]

PD is the second most common neurodegenerative disease, and annual prevalence and incidence in European countries are 257/100,000 and 11–19/100,000, respectively.[3]

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Unlike other neurodegenerative diseases, there are effective treatments for idiopathic PD that relieves symptoms. Medications can improve daily function but cannot modify disease progression. In cases where the drug does not provide a benefit or has significant side effects, advanced treatments such as deep brain stimulation can improve the quality of life. Dopaminergic treatments that improve motor functions generally do not affect non-motor functions such as sensory and mood changes, autonomic dysfunction, sleep disorders, fatigue, and cognitive disorders, and these non-motor symptoms require different medical approaches.[4]

Rehabilitation approaches support medical and surgical treatments. Although there is no consensus in physiotherapy program, increasing evidence shows that physical activity has positive effects on motor (especially walking and balance) and non-motor symptoms through plasticity and improves quality of life, and it is recommended to start a rehabilitation program as early as possible.[5]

The vagus nerve is one of the major elements of the parasympathetic nervous system and plays an important role in the regulation of the immune system as well as vegetative functions.[6] Vagus activation suppresses inflammation through a complex cycle, the cholinergic anti-inflammatory pathway.[7] Moreover, beyond its anti-inflammatory effects, the vagus nerve may also exert analgesic activity through cerebral pathways associated with central pain centers. For this reason, vagus nerve stimulation (VNS), which has been used in refractory epileptic patients for a number of years, has also become a new treatment method in diseases in which various inflammatory processes are shown in the etiology such as inflammatory bowel diseases, musculoskeletal diseases, and autoimmune diseases.[8,9]

The vagus nerve can be stimulated with invasive and non-invasive methods. Implantable VNS (iVNS) involves intermittent electrical stimulation of the nerve with the help of a wire surgically placed around the vagus nerve.[10] iVNS has been approved by the US Food and Drug Administration (FDA) for the treatment of drug-resistant epilepsy and by the FDA and the European Medicines Agency in patients with treatment-resistant depression.[11,12] Non-invasive VNS stimulates the vagus nerve through the ear with a headset and has a lower side-effect profile compared to invasive VNS.[13]

VNS in the treatment of PD is a non-pharmacological intervention with the potential to improve cognition, gait, fatigue, and autonomic functions, but more evidence is needed. The potential mechanisms of VNS in the improvement seen in PD are explained by increased cholinergic transmission, decreased neuroinflammation, and enhanced norepinephrine release.[14] Studies investigating vagal stimulation in PD focused on the efficacy on gastroenteric symptoms, gait, and inflammation, and repeated sessions were reported to be safe and effective on these symptoms.[15,16] Our study, unlike these studies, is about tremor, perhaps the symptom that most affects the quality of life of patients with PD.

Methods

The study protocol was approved by the University of Sisli Hamidiye Etfal Training and ResearchHospital Ethics Committee in accordance with the Declaration of Helsinki (Date: 05.07.2022, Number: 3616). All participants were informed about the study before inclusion and the written consent form was obtained.

This single-center, prospective, implementation study with the before-after design was conducted at the Kanuni Sultan Süleyman Training and Research Hospital, Physical Medicine and Rehabilitation Clinic, between August 2022 and October 2022. Five participants diagnosed with PD who met the inclusion criteria were included in the study. The inclusion criteria were as follows: Age 40–65 years, the medical treatment used for PD has not changed in the past 3 months, and agreement to withhold other therapeutic interventions for upper extremity during the study period.

Four of the initially evaluated participants with PD were excluded from the study due to the exclusion criteria. The exclusion criteria were as follows: Bilateral or unilateral injury history of vagus nerve, presence of another neurostimulator device such as a cardiac pacemaker or deep brain stimulation, presence of a metallic implant near the stimulation area, medical or mental instability, pregnancy, and intervention to the upper extremity in the past 6 months. Participants were instructed not to change the medication time throughout the study. All interventions were administered at the same time of day and after a 12-h overnight withdrawal of medication for PD. Each participant was evaluated twice, before and after the intervention.

Auricular VNS was applied 3 times in total on different days to five participants included in the study. Auricular VNS was performed in the right ear, left ear, and bilaterally. Clinical evaluations of the participants were repeated before and after VNS.

Auricular VNS was performed with a vagustim TENS device with specially designed surface electrodes added in the form of earphones, the size of which can change according to the ear size. The electrodes were placed on the inner and posterior surfaces of the tragus and the concha for both ears. Auricular VNS was performed for 20 min using an asymmetrical, biphasic waveform with a pulse duration of 300 μs and a frequency of 10 hertz. Participants were exam-

ined twice, before and after intervention.

Heart rate and blood pressure were measured before and after each session. The changes in cardiac autonomic functions of the participants were evaluated with Kubios HRV Standard (Version 3.5.0) analysis software (Kubios Ltd., Kuopio, Finland).[17] The tremors of the participants were evaluated clinically with the Unified PD Rating Scale (UPDRS) tremor subscale (sum of items 2.10, 3.15–3.18).[18] In addition, tremor was evaluated quantitatively in three planned planes (X, Y, and Z) before and after VNS using the smartphone application (G-Sensor Logger).[19] This application reports data as a continuous graph like an oscilloscope on three standard axes relative to the ground. The maximum motion in all three axes was recorded. During the measurement, the participants were sitting in a chair with armrests. The smartphone was placed on the dorsum of both hands in patients using an armband. Recordings were taken from both hands separately for 1 minute while the participants rested their forearms on the armrest as comfortably as possible (Fig. 1).

The sample size was calculated using the G*Power version 3.1.9 program (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). According to the sample size calculation, to achieve $\alpha<0.05$ and $\beta=95\%$ according to the effect size of 2.59, it was calculated that a minimum of five participants would be required for the study as described Rocha et al.[20]

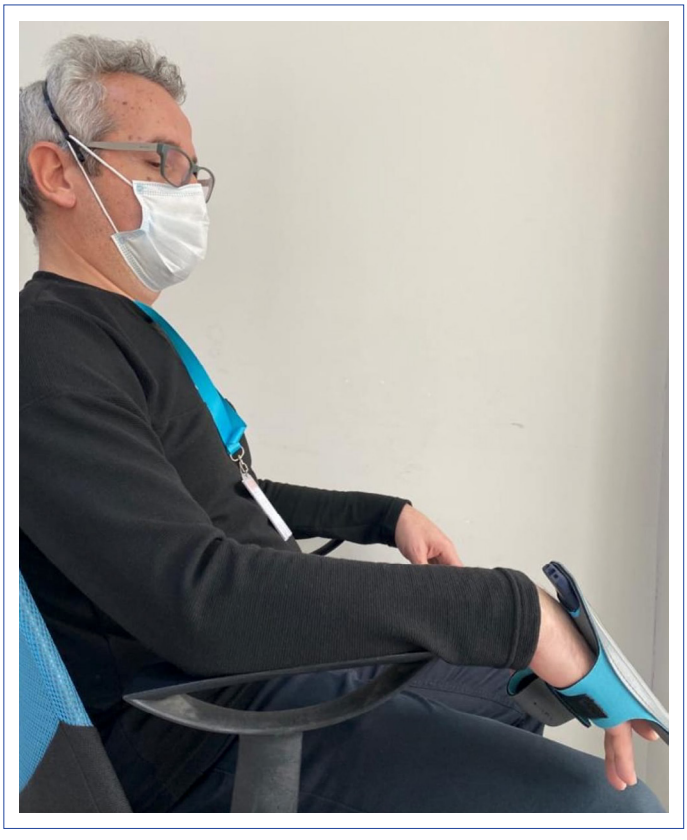

Figure 1. Measuring tremor with a smartphone.

The IBM SPSS for MacOS v. 21.0 (IBM Corp., Armonk, NY, USA) was used for analysis. For intra-group analysis, the paired-sample t-test or Wilcoxon signed-ranks test was used and was used according to the distribution of the variables. Descriptive statistics were presented as mean (standard deviation) and median (minimum and maximum) values. The confidence interval was 95% and $p<0.05$ was considered statistically significant. In addition, statistical significance was considered as $p<0.0167$ for the analysis using Bonferroni correction, if necessary.

Results

Ten participants with PD who visited to Physical Medicine and Rehabilitation clinic were evaluated for eligibility. Six of them were selected for the participation in the study. One participant was dropped out during after-treatment evaluation. Demographic and clinic characteristics are shown in Table 1.

According to intra-group analysis, there were only significant differences in terms of SNS index for the left-side application and X max values (for tremor at the left hand) for bilateral application ($p=0.043$) (Tables 2 and 3).

Based on the comparison of the changes between before and after treatment results between three application sides, there was a significant difference at the Y max value for left-hand tremor, and according to post hoc analysis, it was found that there was a significant difference between right hand and bilaterally application of the VNS ($p=0.009$) (Tables 2 and 3).

Discussion

In this study, non-invasive auricular VNS applied to patients with PD was found to reduce hand tremor amplitude evaluated in a 3D plane through a smartphone application.

VNS can be performed invasively (through a surgically implanted device) or non-invasively (transcutaneously). Non-invasive VNS is safer in terms of side-effect profile since it does not require an additional surgical intervention. Non-invasive VNS is performed with electrical stimulation from the external ear canal or neck.[21] Non-invasive auricular VNS was used in this study.

In studies, the effectiveness of VNS was investigated in cardiovascular diseases such as heart failure and arrhythmia; gastrointestinal tract diseases; psychiatric disorders such as panic disorder, depression, and post-traumatic stress disorder; and neurological conditions such as epilepsy, migraine, stroke, PD, and dementia.[22]

In a study investigating the cardiovascular effects of VNS,

Table 1. Demographic and clinical characteristics of the participants

	Participants (n=5)	Min	Max
Age (year), Mean (SD)	64.0 (9.3)	50.0	75.0
Gender, n (%)			
Female	2 (40%)	-	
Male	3 (60%)	-	
BMI (mean (SD))	30.5 (3.7)	26.4	34.5
Disease duration (month) Mean (SD)	64.4 (63.4)	6	172
H&Y stage, Mean (SD)	2.0 (0.7)	1.5	3
Stage 1	-		
Stage 1.5	3		
Stage 2	-	-	-
Stage 2.5	1		
Stage 3	1		
Tension, Mean (SD)			
Systolic	122.2 (18.0)	90	132
Diastolic	66.4 (10.9)	50	78
Pulse (beats per minute)			
Mean (SD)	74.0 (8.9)	64	86

SD: Standard Deviation; min: minimum; max: maximum; BMI: Body Mass Index; H&Y: Hoehn & Yahr.

Table 2. Within and between group analysis of the tension, pulse, and cardiac parameters according to the application side of VNS

Variables Mean (SD)	Right side (n=5)			Left side (n=5)			Bilaterally (n=5)			
	pre-T	post-T	p^a	pre-T	post-T	p^a	pre-T	post-T	p^a	p^b
Tension (systolic)	122.2 (18.0)	120.2 (8.4)	0.686	132.4 (22.9)	122.2 (26.5)	0.461	127.6 (19.4)	119.4 (14.4)	0.138	0.504
Tension (diastolic)	66.4 (10.9)	69.4 (8.0)	0.588	72.0 (18.8)	71.8 (16.8)	0.893	70.4 (11.1)	65.6 (11.9)	0.043*	0.163
Pulse	74.0 (8.9)	71.8 (12.3)	0.498	73.2 (9.9)	70.6 (8.4)	0.336	70.0 (15.0)	69.0 (10.0)	1.000	0.715
Cardiac parameters										
RMSSD	325.6 (372.1)	110.8 (55.4)	0.225	34.2 (21.6)	38.1 (23.7)	0.500	179.7 (278.7)	172.1 (292.1)	0.684	0.415
Stress Index	4.7 (3.5)	9.4 (7.0)	0.138	12.1 (4.4)	9.5 (1.4)	0.416	8.3 (6.4)	9.9 (6.4)	0.225	0.131
PNS Index	39.40 (74.5)	1.81 (1.6)	0.225	−0.59 (1.0)	−0.29 (1.0)	0.500	3.57 (7.7)	3.48 (8.1)	0.686	0.432
SNS Index	−1.45 (2.3)	0.08 (1.4)	0.225	0.89 (1.1)	0.01 (1.00)	0.0.43*	0.02 (1.90)	0.09 (1.7)	0.893	0.061
LF	43.5 (28.6)	32.4 (23.2)	0.686	52.8 (20.1)	48.1 (23.3)	0.686	40.7 (33.3)	55.5 (21.7)	0.138	0.512
HF	40.9 (35.1)	62.5 (27.5)	0.345	29.3 (26.2)	42.1 (23.3)	0.138	53.2 (33.8)	39.8 (23.2)	0.500	0.275
LF/HF	2.5 (2.6)	0.9 (1.3)	0.686	4.9 (6.5)	3.1 (5.0)	0.080	4.9 (9.6)	4.2 (7.0)	0.893	0.566

SD: Standard Deviation; T: Treatment; RMSSD: The Root Mean Square of Successive Differences between normal heartbeats; PNS Index: Parasympathetic Nervous System Index; SNS index: Sympathetic Nervous System Index; LF: Low Frequency; HF: High Frequency; p^a: significance value for within group analysis (Wilcoxon's Signed ranks test); p^b: the significance value of the difference in change before and after in the three groups (Kruskal Wallis test), *: $p<0.05$ is considered the significance.

it was found that there was a decrease in left ventricular contractility and heart rate.[23] Similarly, in this study, it was determined that the diastolic blood pressure of the participants decreased significantly after VNS. The right-sided cervical vagus nerve innervates the sinoatrial node, and the left-sided cervical vagus nerve innervates the atrioventricular node. Due to this innervation, the right-sided VNS is considered to be more risky in terms of cardiovascular side effects, and left-sided VNS is generally used in studies.[24] A study comparing the cardiovascular effects of right, left, and bilateral stimulation in auricular VNS could not be found in the literature. In the present study, no difference was found between the three applications in terms of cardiovascular side effects.

Non-invasive VNS has been used in the treatment of epilepsy for more than 30 years. Information on the system's safety and side-effect profile is available. In a meta-analysis, side effects of non-invasive VNS were reported as skin ir-

Table 3. Within and between group analysis of the tremor parameters according to the application side of VNS.

Variables	Right side (n=5)			Left side (n=5)			Bilaterally (n=5)			
Mean (SD)	**pre-T**	**post-T**	**p[a]**	**pre-T**	**post-T**	**p[a]**	**pre-T**	**post-T**	**p[a]**	**p[b]**
Tremor (right)										
Xmax	8.9 (10.0)	3.4 (1.3)	0.345	4.5 (1.1)	4.6 (2.6)	0.893	3.6 (0.9)	5.4 (2.3)	0.225	0.208
Ymax	7.9 (3.0)	6.8 (1.4)	0.345	8.1 (2.7)	8.5 (1.9)	0.686	7.0 (1.4)	8.7 (2.7)	0.138	0.196
Zmax	15.5 (7.7)	14.2 (1.6)	0.500	13.3 (0.6)	14.8 (6.2)	0.893	12.6 (1.0)	12.1 (2.3)	0.686	0.632
Tremor (left)										
Xmax	3.7 (0.8)	3.8 (1.4)	0.893	4.4 (1.6)	4.2 (2.2)	0.893	3.7 (2.4)	5.7 (1.8)	0.043*	0.113
Ymax	7.5 (2.2)	7.5 (3.0)	0.893	6.8 (2.5)	6.4 (1.4)	0.500	7.5 (2.8)	6.6 (2.3)	0.080	0.014*
Zmax	12.7 (0.4)	12.1 (0.8)	0.080	13.5 (1.6)	13.2 (1.3)	0.500	16.0 (2.8)	14.8 (2.1)	0.225	(R-L:0.028 R-B:0.009** L-B:0.347) 0.417
UPDRS Tremor Subscale	11.0 (1.6)	11.0 (1.6)	1.000	10.2 (1.5)	10.6 (1.5)	0.157	11.0 (1.6)	10.8 (1.3)	0.317	0.300

SD: Standard Deviation; T: Treatment; UPDRS: Unified Parkinson's Disease Rating Scale; p[a]: significance value for within group analysis (Wilcoxon's Signed-ranks test); p[b]: the significance value of the difference in change before and after in the three groups (Kruskal–Wallis test), *: p<0.05 is considered significance.; ** post hoc analysis for Kruskal–Wallis test (Mann–Whitney U-test/p<0.0167 is considered significance for post hoc analysis.

ritation, headache, nasopharyngitis, syncope, nausea, and vomiting.[25] No undesirable effects were observed during or after the non-invasive VNS applied to the participants included in our study.

The use of VNS in different neurological diseases has become widespread recently. In a randomized clinical study investigating the efficacy of VNS in patients with chronic ischemic stroke, significant increases were found in upper extremity functions, activities of daily living, and quality of life of the participants in the VNS group.[26] In a meta-analysis evaluating the effects of VNS in stroke patients, a similar increase was found in the functional levels of the participants and it was stated as a safe treatment method.[27] These positive effects are thought to be related to the induction of neuroplasticity by molecular and neuronal mechanisms as a result of VNS application.[28] More studies are needed to examine the neuroplasticity changes that occur with VNS application. In a short report examining the effectiveness of VNS in patients diagnosed with multiple sclerosis, positive effects on cerebellar tremor and dysphagia were reported in three patients. Positive effects are thought to occur with neuroplasticity and cerebellar activity, similarly.[29]

In this study, non-invasive VNS application was applied as 20 min per session, 0.8 mA, frequency 10 Hz, pulse width 300 μs, and biphasic rectangular pulse. Non-invasive VNS application parameters differ between studies. In the studies, the pulse width was used between 100 μs and 4 ms, frequency between 2 and 300 Hz, and current between 0.2 and 10 mA.[30] More studies are needed to determine the optimal non-invasive VNS administration route, frequency, duration, and parameters.

In a randomized, sham-controlled, double-blind study exploring the effectiveness of non-invasive VNS in PD, it was found that motor and non-motor functions of the patients improved, there was a decrease in proinflammatory cytokines, and no undesirable effects were observed.[31]

Tremor, one of the main motor symptoms of PD, is seen in 75% of patients. Resting tremor is usually detected in the upper extremity, and the pathophysiology of tremor is not clearly understood. It is thought that not only dopaminergic pathways but also different mechanisms play a role in the development of tremor.[32] Compensatory strategies, drug therapies, and surgical interventions are used in the treatment of tremor.[33] Considering the side effects and efficacy of drugs and methods used in the treatment of tremor, there is a need for effective and safe methods in treatment. After non-invasive VNS applied to the participants included in this study, reductions in tremor measured in the three-dimensional plane were detected. There is a need for more studies investigating the effectiveness of non-invasive VNS in the treatment of tremor.

Tremor in PD is mostly evaluated with UPDRS. In addition, it is also possible to quantitatively evaluate tremor with video recording, additional sensors, smartphone, and smart watch applications.[34] However, the UPDRS has limitations such as being dependent on the evaluator and experience. Therefore, there is a need for a reliable and evaluator-inde-

pendent measurement method in the evaluation of tremor in PD.[35] In this study, a smartphone was placed on the patients' hands and the G-Sensor Logger program was used for tremor measurement. The mean and maximum tremor values were recorded for 1 min in the 3D plane for each hand. These systems, which offer the opportunity to evaluate tremor quantitatively, are inexpensive, accessible, and objective. Although tremor is considered a measurable movement disorder, there is currently no generally accepted measurement method.[36]

According to our knowledge, this is the first study to evaluate the efficacy of VNS on tremor in PD. The limitations of the study are the absence of a control group, the small sample size, and the evaluation of only acute effects of non-invasive VNS. Future studies with a larger number of participants, a sham-control group, and investigating the long-term effects of VNS are needed.

Conclusion

In this study, although no change was detected in clinical tests in the evaluation of tremor in PD after non-invasive VNS, a decrease in tremor was detected in quantitative measurements, and no undesirable effects were observed. However, more studies are needed on the efficacy and safety of VNS in PD.

Disclosures

Ali Veysel Ozden, one of the researchers, is the medical director of Vagustim company and the company provided the devices used in this study.

Ethics Committee Approval: Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee, Approval dated 05.07.2022 and numbered 3616.

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