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Functional Impact of Aerobic Exercise on Cardiovascular Autonomic Function, Peripheral Neuropathy Gait and Balance, Depression, and Quality of Life in Parkinson Disease.

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ABSTRACT

Background: Parkinson's disease (PD) is a progressive neurological disorder marked by the degeneration of neurons that produce dopamine in the substantia nigra area. This results in symptoms such as tremors, rigidity, bradykinesia, and difficulty maintaining balance. These symptoms significantly affect the individual's quality of life.

Aim of the work: We aimed to assess the functional impact of aerobic exercise on cardiovascular autonomic function, peripheral neuropathy (gait and balance), depression, and quality of life in Parkinson's disease.

Patients and Methods: The current investigation is a two-arm parallel randomised controlled trial. The sample was chosenusinga non-probabilistic method.Arandom1:1 ratio was used to assign the candidates to one of the 2 groups:25 case in the exercise interventions group and 25 case as control group (no invasive intervention).

Result: As regard motor "Nerve conduction study" of popliteal and Tibialis nerve at both lower limbs, Na+/I− symporter (NISL) score, "Brain-derived neurotrophic factor"(BDNF), quality of life score, "Beck Depression Inventory" (BDI) score there was insignificant differences between two groups at baseline however, after six weeks, a marked improvement was noted in interventional group vs control.

Conclusion: It was found that aerobic activity could lead to enhancements in motor NCV inpopliteal fossa, and Tibial nerve, sural sensory nerve NCV, TINETTI gait and balance test, clinical neuropathy score, NIS L score, BDNF, quality of life score, BDI score.

Keywords: Aerobic Exercise, Cardiovascular Dysfunction, Peripheral Neuropathy, Depression, Parkinson Disease.

INTRODUCTION

"Parkinson's disease" (PD) is aneuro logical disorder that is more common in theaging people, with higher rates of occurrence and development. The primary motor manifestation of PD include brady kinesia (slowness of movement), postural instability, tremors, and stiffness. These symptoms lead to a decrease in functional abilities, particularly when combined with an inactive lifestyle [1]. Autonomic nervous system malfunction can lead to alterations in blood pressure, even in the initial phases of PD [2].

Various detectors can determine the functioning of the autonomic nervous system by measuring its influence on the cardiovascular system through "Ambulatory Blood Pressure Monitoring (ABPM) and continuous 24-hour Holter monitoring. Autonomic nerve system malfunction can lead to blood pressure fluctuations even in the initial phases of PD, orthostatic hypotension, as well as postprandial, nocturnal, and supine hypotension can occur when the autonomic dysfunction established [3].

24 hours Holter monitoring is a diagnostic method that is used to monitor and assess the autonomic nervous system. It is a reliable and easily observable tool for early detection and follow-up. Individuals who areimpacted may also display non-motor symptoms, including cognitive decline, sleep disturbances, autonomic dysfunction, depression, anxiety, fatigue, and lack of motivation. These symptoms have a substantial impact on the overall quality of life and can hinder one's ability to engage in physical exercise programs or leisure activities [4].

Patients with PD frequently experience peripheral neuropathy. The incidence of marginal neuropathy in individuals with PD varies from 4.8% to 55%, while it is 9% among the overall population. The causal relationship between peripheral neuropathy and reduced motor function in PD, leading to compromised mobility and heightened balance deficits, remains uncertain [5].

Patients with PD frequently experience depressive problems, which have a significant impact on various clinical features of the condition. In addition to creating underly in gemotion a languish, depressive disorder significantly impact life quality, motor and intellectual impairments, functional disability, and other mental comorbidities in individuals with PD [6].

Previous studies showed that exercise can potentially influence the progression of PD by interacting with the neurodegenerative process. This interaction is believed to be facilitated by brain derived neurotrophic factor (BDNF) [7].

Physical exercise could be effective as non-pharmacological intervention for patients with PD, preventing the decrease in functional capacity and enhance their quality of life. Aerobic exercise (AE) has been demonstrated to be a significant stimulus for enhancing both physical and mental well-being, as well as inducing anatomical modifications in the brain [8].

Thus, AE has the capacity to decelerate, disrupt, or potentially reverse the advancement of PD, while fostering neuroplasticity by adapting damaged signalling pathways. Several systematic evaluations in the literature examine the efficacy of physical workouts in enhancing both motor and non-motor symptoms in patients with PD. [9].

This work aims to assess the functional efficiency of AE on cardiovascular autonomic function, peripheral neuropathy (gait and balance), depression, and quality of life in Parkinson disease.

Patients and Methods

The present investigation is a two-arm parallel design study with randomly allocated participants to two treatment groups. The sample was selected using a non-probabilistic methodology. The participants were assigned in a random manner, with an equal number being allocated to both the workout group and the control group (without any invasive intervention).

Study setting

randomized controlled trial conducted between Beni-Suef Faculty of Medicine, Egypt and Al-Azhar University Hospitals.

Inclusion criteria

Volunteers are required to possess a clinical diagnosis of Parkinson's disease, which must be verified by a neurologist who is acknowledged by the board. The diagnosis must adhere to the criteria established by the UK Brain Bank, and the volunteers must be aged 60 years or older. Furthermore, it is recommended to classify them according to the Hoehn and Yahr scale, ranging from 1 to 3. Volunteers must maintain a consistent pharmacological therapy regimen for at least 30 days before they can take part in the trial.

Exclusion criteria

Exclusion criteria for the study included cognitive impairment as measured by the adjusted Mini-Mental State Examination for the educational level of the study group. Exclusion criteria included a history of cardio respiratory, neuromuscular, musculoskeletal, peripheral sensory neuropathy, diabetes, or any other medical condition. Furthermore, individuals who did not have their diabetes or hypertension under control were not included in the study.

Sample size

The G Power tool version 3.1 was used to calculate the sample size for the study. This was done with a 95% confidence level and 80% study power in order to determine the number of participants needed. The computation relied on a preliminary study (not yet published) that took into account the LF/HF index of HRV and systolic blood pressure (SBP). The optimal sample size for each group to detect a decrease in SBP, assuming an effect size of 0.80, was determined to be 19 volunteers. Thus, taking into account the potential occurrence of dropouts, a total of 25 participants were registered for each group.

Verbal consent

The researcher was responsible for reaching out to possible participants and inviting patients to take part in the study. They discussed the study's aims, the criteria for inclusion and exclusion, the roles of the participants, as well as the risks, rewards, and ethical considerations involved. After agreeing to take part in the study, participants were requested to sign two copies of an informed consent form, one for themselves and another for the researcher.

Methods

All participant shad the following:

Comprehensive chronicle: Required information includes the individual's name, age, gender, length of illness, presence of any other medical conditions, and history of medication usage. A comprehensive evaluation was conducted to examine both the overall and specific condition. Cardiac autonomic function is evaluated through the use of ABPM and 24-hour Holter monitoring, specifically by analyzing heart rate variability.

Interventions

Physical exercise program at physiotherapy and rehabilitation department clinics The physical activity sessions consisted of :

1) During the 5-minute warm-up, patients stretch their main muscle groups in their upper and lower limbs as well as their trunk.

2) Duringthe30-minute aerobic exercise (AE), patients walk continuously on level surface sand hills at an intensity ranging from 40 to 60% of their heart rate reserve.

3) Cool down (5minutes): Perform stretching exercises targeting the primary muscle groups used during the sessions, promoting relaxation.

At the conclusion of the 6-week intervention program, the patients were asked to specify if they believed they had received a placebo or an active treatment. In addition, participants were requested to assess their level of confidence using a scale ranging from 0 to 10, where 0 represents no confidence and 10 represents a high level of trust in obtaining the active therapy. Out comes assessment “Peripheral neuropathy” investigation

Clinical assessment

The clinical signs and symptoms indicative of peripheral neuropathy were assessed using two scales to determine their existence and severity. The NIS-LL assesses the strength of muscles, the ability to perceive touch pressure and vibration, the reflexes of tendons, and the position of joints in the lower limbs. The scale is adjusted based on age, so that diminished ankle reflexes are considered normal or non-existent in individuals aged 70 years or above.

Participants who scored between 3 and 5 points on the NIS-LL scale for reflexes and sensory functions were classified as having slight neuropathy indicators. Neuropathy symptoms were categorised as moderate for individuals with scores between 6 and 8, and severe for those with scores between 9 and 10.

The “Modified Toronto Clinical Neuropathy Score” (mTCNS) is utilised to collect data on participants' subjective assessment of discomfort andsigns of neuropathy, specifically foot pain, tingling, impassivity and weakening. Individuals who had a cumulative score of 6 or higher were classified as displaying symptoms of peripheral neuropathy.

Nerve conduction velocity

Surface recording electrodes were used to undertake sensory and motor nerve conduction tests, following conventional placement. The assessment was conducted on the lower extremities, specifically examining the sural sensory, peroneal motor, medial plantar, and tibial motor nerve conduction investigations, which also included F-waves. The assessment was expanded to include the evaluation of the upper limbs, focusing on the “ulnar and median sensory” and “motor nerve conduction” tests, as well as the radial sensory nerve conduction studies, if any of the previous potentials were found to be lower than the standard thresholds. In the event that neither the sensory nor the motor nerves indicated any activity, investigations were conducted on the corresponding nerve on the other side using nerve conduction.

Diagnostic criteria for peripheral neuropathy

The participants were identified with big fiber neuropathy through the utilization of nerve conduction testing.

In the case of small fiber neuropathy, individuals were diagnosed if they exhibited anomalies in a minimum of two of the following examinations:

(i) The sensory component including touch pressure, pinprick, vibration, and joint position) of the NIS-LL scale must have a score of 1 or higher, and/or certain items from the mTCNS scale must have a score of 1 or higher. These specific items are foot pain, tingling, numbness, and temperature.

(ii) The foot's abnormal sensitivity to warm and/or cool temperatures is evaluated using Quantitative Sensory Testing (QST), with a threshold that is equal to or greater than the 97th percentile when compared to normative data from healthy individuals of the same age and sex.

Blood pressure variability

The recording of 24 h ABPM was conducted. The measurement of ABPM was taken every quarter of an hour during the day and every half of an hour during the night. For each time period - 24 hoursdaytime, and nighttime - the standard deviations (SDs) of the SBP and diastolic blood pressure (DBP) were calculated. The standard deviations of each time were examined as an indicator of blood pressure variability.

Tertiles of twenty- four-hour SBP and DBP were estimated because there is no clear threshold to classify people as having high or Low blood pressure variability (BPV). The categorization of Dipper profiles was based on theextent of nocturnal SBP reduction.

Twenty-four-hour ambulatory ECG monitoring (Holter monitoring)

Holter monitoring was employed for the purpose of monitoring electrocardiogram (ECG) activity continuously over a period of 24 hours. Patients were able to engage in regular daily activities throughout the 24-hour Holter testing period. The HRV analysis involved the evaluation of Holter recordings from all patients, where artefacts were manually removed. Subsequently, HRV variables were computed automatically.

The present study examined time-domain measures of "Heart Rate Variability" (HRV), specifically focusing on the Standard Deviation (SD) of all normal-normal (NN) intervals (SDNN), the average of NN intervals during all 5-minute periods that make up the24-hour day (SDANN), SDNN indices, and the consecutive normal-normal differences (SDSD).

The analysis also included the examination of pNN50, which represents the percentage of NN intervals that differ by more than 50 msec from each other. Additionally, the study examined root mean square of successive normal-to-normal interval differences (RMSSD). The HRV triangular index, which is calculated by dividing the integral of the density distribution (number of all NN intervals) by the maximum of the density distribution, was also analyzed.

Gait and balance assessment

Assessment of gait and balance was conducted both when the medicine was being taken and when it was not.12 hours following their last dose of L-DOPA, the study participants were evaluated in the morning when theywere not taking any medication.

They underwent testing while under the influence of L-DOPA one to three hours following their initial dose on the same day. Inertial measuring units (IMUs) from Hasomed GmbH, specifically three synchronized Reha Gait models, were distributed to the subjects. A tri-axial gyroscope and an accelerometer, both with a 100 Hz sampling frequency, made up each IMU.

Ankles and the side of each foot were where the inertial measurement units (IMUs) were placed. Both a 20- meter straight walk and a 10-80-degree circular walk were used to assess gait.

The second experiment was carried out in the left and right directions on a 1.2 m diameter carpet. Additionally, the TUG test was administered. Forth epurpose of assessing postural control, subjects performed a series of 30-second trials in the following positions: tandem on the floor, side-by-side on foam, with and without eyes closed, and with and without eyes open.

The verified methods were utilized to extract the subsequent gait parameters: Metrics obtained from the subsequent sources: The obtained data encompasses measurements of linear and curved ambulation, including stride duration, step rate, variability in walking pattern, walking velocity, length of each stride, as well as the angles at which the heel strikes and the toe lifts off the ground.

Data pertaining to the "Timed Up and Go" (TUG) test is also recorded; this data includes details regarding the length of turns and the maximum "angular velocity" attained while turn. The study also collects data on static balancing, which includes jerk, acceleration, velocity, and sway area in both the "Anterior-Posterior (AP) and medio-lateral (ML) directions. We calculated the "Medial-Lateral" (ML) and AP orientations because these have been demonstrated to represent distincmedical conditions or the body's compensating mechanisms.

Depression

Evaluate depression using the "Beck Depression Inventory" (BDI) score. It comprises of 21 items, with each item being assigned a score ranging from 0 to 3. These items are designed to evaluate the clinical symptoms associated with depression disorder. The BDI was initially developed as a tool to measure the severity of depressive symptoms in a study focused on evaluating specific psychoanalytic theories of depression in patients with different psychotic, psychoneurotic, and anxiety disorders.

Hematological sampling and analysis of biochemical parameters

Blood samples were obtained in the morning before the clinical evaluation. The blood samples were spun in a centrifuge for 10 minutes at 1,000 times the acceleration of gravity. Subsequently, the serum was extracted and preserved at a temperature of -20°C until the BDNF analysis was conducted. The blood samples from the control

group were handled using identical procedures. The levels of brain-derived neurotrophic factor (BDNF) in blood serum were quantified using sandwich enzyme-linked immune sorbent assay (ELISA) kits provided by the manufacturer. This measurement was performed in both the diseased and control groups (DuoSet, R&D Systems, Minneapolis, MN, USA).

Two separate analyses were performed on each sample. The minimum detectable concentration in the tests is10 pg/ml. Briefly, each well was supplemented with diluted capture antibody (with a manufacturer-specified concentration) in phosphate-buffered saline (PBS). Overnight, the mixture was left to incubate at 4 degrees Celsius. Sigma, St. Louis, MO, USA, supplied the PBS that contained 0.05% Tween 20, which the plate was washed four times. The plate was incubated at room temperature for 2 hours after being blocked with a solution containing 1% bovine serum albumin. Subsequently, it underwent four rounds of washing using a solution consisting of PBS and 0.05% Tween20.

After introducing the samples and standards, the plate was placed inan incubator programmed to maintain a temperature of 4 degrees Celsius during the night.

After the plates were washed, the detection antibody was added to a diluted solution of PBS according to the manufacturer's instructions.

After two hours of room temperature storage in an incubator, the plate was transferred to the next step. Strepavid in (Duo Set R&D Systems, Minneapolis, MN, USA) was added to the plates after washing them, and they were left to incubate for 30 minutes. A 15-minute period was then allowed for the reaction to proceed without light after o-phenyl enediaminecolour reagent (Sigma, St. Louis, MO, USA) was added to each well. The reaction was halted by adding 1 M H_2SO_4 to each well. The absorbance was measured using a plate reader at a wavelength of 492 nm (Emax, Molecular Devices, Minneapolis, MN, USA).

A study was undertaken assessing the amounts of vitamin B12 and folic acid. Vitamin B12 insufficiency was diagnosed if its levels were lower than 191 pg/l, or if folate levels were less than 500 pg/l. An immunoassay system developed by Beck man Coulter, Inc., known as Access2, was used to measure the amounts of folate and vitamin B12 in the serum.

A "competitive-binding receptor" assay was employed to determine folate levels. This assay utilized a pair of proteins, namely a "folate - antifolate binding protein pair", together with paramagnetic particles that were connected to a "goat anti-mouse capture antibody". The vitamin B12 level was measured using a competitive - binding immune-enzymatic assay that utilized a monoclonal mouse anti body pair, specific to intrinsic factor and anti-intrinsic factor, which were attached to paramagnetic particles.

Quality of life assessment

The study utilized the PDQ-39 questionnaire, developed by Peto et al. [10].This tool is readily accessible on the internet for the purpose of conducting research. There are 39 questions on the form, and each one has a five- point scale: never, some times, often, and always.

The measure comprises eight factors: physical mobility, social support, psychological health, cognitive impairment, communication, and bodily discomfort. The scores were transformed into a numerical scale ranging from 0 to 100. A higher score was indicative with a lower quality of life.

As a result of implementing mandatory completion for all items, there was no missing data observed in any of the subscales, indicating a 0% rate of missing data. Following translation, the PDQ-39's internal consistency reliability was found to be.89 astested by Cronbach's alpha. The subscale shad Cronbach's alpha values between

0.78 and 0.94.

The results were assessed at two specific time points: (1) baseline, which refers to the period before the intervention program began, and (2) after 6 weeks intervention, which corresponds to atime frame of 48 hours to 1 week following the last intervention session.

Statistical Analysis

The information was input in to a computer system and examined with the help of IBM SPSS soft ware, version 20.0. The geographical location of the corporation is Armonk, New York, and the name of the company is IBM Corporation. Numerical values and percentages were used to depict the quantitative data.

The Shapiro-Wilk test was used to confirm the normality of the distribution. The quantitative data were analyzed using statistical measures such as the range (minimum and maximum values), mean, standard deviation, median, and inter quartile range (IQR). The statistical significance of the obtained results was assessed using a significance level of 5%.

The used tests were

1 - Chi-square test: For categorical variables, to compare between different groups

2 - Fisher's Exact correction: for Correction for chi-square when more than 20% of the cells have expected count less than 5

3 - Student t-test: For normally distributed quantitative variables, to compare between two studied groups.

4 - Paired t-test: For normally distributed quantitative variables, to compare between two periods

5 - Mann Whitney test: For not normally distributed quantitative variables, to compare between two studied groups

RESULTS

Neither the exercise intervention group nor the control group showed any statistically significant differences in terms of demographic data, disease duration, HOEHN and YAHR stage in the off state, and movement disorders. Patients getting medication that affects the neurotransmitter dopamine, namely levodopa equal dose, and those undergoing advanced therapy in Montreal. Cognitive performance, the average number of sessions in the interventional group was 2.12.

Regarding the NCV in motor nerves of both lower limbs Initially, there were no notabled sparities between the two groups. However, after 6 weeks, the interventional group demonstrated a significant enhancement in comparison to the control group, as seen by the data presented in Table 1.

Initially, no significant disparities were identified between the two groups in terms of sensory NCV. After a duration of 6 weeks, the interventional group exhibited a significant enhancement in comparison to the control group, as evidenced by the data presented in table 2.

During the first phases of the TINETTI gait and balance test trial, both groups showed no significant differences. After a duration of 6 weeks, the intervention group exhibited a significant enhancement in comparison to the control group, as indicated by the data presented in table 4.

Regarding gait, there were no notable alterations seen between the two groups. at the beginning. However, after 6 weeks, the interventional group exhibited a significant enhancement in comparison to the control group, as indicated in table 5.

Regarding the clinical neuropathy score, Initially, there were no notable disparities between the two groups atthe beginning of the study. However, after 6 weeks, there was a substantial improvement in the interventional group compared to the control group, as indicated in table 3.

Regarding the NIS L score, there were no significant differences between the 2 groups at the beginning of the study. However, after 6 weeks, there was a substantial improvement in the interventional group compared to the control group, as indicated in Table 7.

There were no notable disparities in the quality of life score between the two groups at the beginning of the study. Nevertheless, after a durationof6 weeks, the interventional group exhibited a significant enhancement in comparison to the control group, as indicated by the data presented in Table 8.

Regarding the BDI score, there were no significant differences between the two groups at the beginning of the study. However, after 6 weeks, there was a substantial improvement in the interventional group compared to the control group, as seen in Table 9.

Regarding BDNF, there were no notable alterations seen between the two groups. at the beginning of the study. After a duration of 6 weeks, the intervention group exhibited a significant improvement in comparison to the control group, as evidenced by the data presented in Table 10. Table 11 shows a significant decrease in the intervention group compared to the control group in terms of folic acid and Vitamin B12.

The diurnal blood pressure rhythm in the group with PD was significantly distinct from that in the control group ($p < .05$). The PD group had the largest rate of reverse dipping, while the control group had the highest proportion of non-dipping. However, there were no notable alterations seen between the two groups in terms of 24-hour blood pressure, as seen in table 12. Heart rate variability was significant difference between two groups as shown in table13

Table1. Comparison between the two studied groups according to Motor NCV

	Motor NCV	Interventions (n= 25)	Control(n=25)	t	P
Ankle fibular head (m/s)	**Baseline**				
	Min.–Max.	39.0– 48.0	39.0– 49.0	0.388	**0.700**
	Mean±SD.	44.20± 3.03	44.52± 2.80		
	Median(IQR)	44.0(42.0–47.0)	45.0(44.0–46.0)		
	After6weeks				
	Min.–Max.	39.0– 43.0	39.0– 49.0	5.586*	**<0.001***
	Mean±SD.	41.08± 1.15	44.28± 2.62		
	Median(IQR)	41.0(40.0–42.0)	44.0(44.0–45.0)		
	t_0 (p_0)	5.076*(<0.001*)	1.809 (0.083)		
Fibular head–popliteal fossa (m/s)	**Baseline**				
	Min.–Max.	40.0– 47.0	39.0– 49.0	0.055	**0.956**
	Mean±SD.	43.32± 2.30	43.36± 2.83		
	Median(IQR)	43.0(42.0–45.0)	43.0(42.0–45.0)		
	After 6 weeks				
	Min.–Max.	39.0– 43.0	39.0– 48.0	5.031*	**<0.001***
	Mean±SD.	40.48± 1.36	43.84± 3.05		
	Median(IQR)	40.0(39.0–41.0)	43.0(42.0–47.0)		
	t_0(p_0)	8.122*(<0.001*)	0.857 (0.400)		
Tibialis nerve (m/s)	**Baseline**				
	Min.–Max.	40.0– 44.0	40.0– 45.0	0.091	**0.928**
	Mean±SD.	41.92± 1.32	41.96± 1.74		
	Median(IQR)	42.0(41.0–43.0)	42.0(41.0–42.0)		
	After6weeks				
	Min.–Max.	36.0– 41.0	40.0– 44.0	6.939*	**<0.001***
	Mean±SD.	38.60± 1.35	41.52± 1.61		
	Median(IQR)	39.0(38.0–39.0)	41.0(40.0–43.0)		
	t_0 (p_0)	**12.949*(<0.001*)**	**2.400*(0.024*)**		

Table2. Comparison of sensory NCV between the two studied groups

SensoryNCV(m/s)	Interventions (n=25)	Control (n=25)	T	p
Baseline				
Min.–Max.	46.0– 50.0	45.0– 51.0	0.383	**0.704**
Mean±SD.	48.20± 1.44	48.04± 1.51		
Median(IQR)	48.0(47.0–49.0)	48.0(47.0–49.0)		
After6weeks				
Min.–Max.	48.0– 55.0	45.0– 50.0	7.855*	**<0.001***
Mean±SD.	51.48± 1.94	47.52± 1.61		
Median(IQR)	52.0(50.0–53.0)	48.0(46.0–49.0)		
t_0(p_0)	**10.284*(<0.001*)**	**3.641*(0.001*)**		

Table3. Comparison between the two studied groups according to Neuropathy scale

Perspectives Scale	Interventions (n=25)	Control (n=25)	F	p
Baseline				
Min.–Max.	23.0– 33.0	23.0– 44.0	22.5	**<0.001***
Mean±SD.	28.12± 2.5	37.3± 5.4		
Median(IQR)	28.0(27.0–29.0)	41.0(40.0–42.0)		
After 6 weeks				
Min.–Max.	30.0– 41.0	30.0– 53.0	21.9	**<0.001***
Mean±SD.	36.21± 3.30	46.52± 4.61		
Median(IQR)	35.0(34.0–36.0)	50.0(50.0–52.0)		
F_{crit} (p_0)	**1.866* (<0.001*)**	**1.860* (<0.001*)**		

Perspective SCALE is A tool for measuring perspective. Here, 10 questions were asked, including a group of questions related to negative aspects, and questions related to positive aspects. A Likert scale was used to determine the grades, where the answer was strongly agree = 5 degrees, agree = 4 degrees, neutral = 3 degrees, and disagree 2 degrees, and 1 degree for strongly disagree, and the scores were reversed for the negative perspectives, The scores of all items were then summed for each participant to obtain a total score for each individual. The average score was calculated the results were as shown in the table, indicating an improvement in the scale...by 20%, as the average of the scale was 28 before and 35 after the 6 weeks, and it was theminimum value of the scores for the group. The initial temperature is 23 and the maximum is 33 degrees, changing after 6 weeks to 30 degrees for the minor and 41 for the major. From the values of the coefficient of variation and... it becomes clear how accurate and important the data are and that they are statistically significant.

Table4. Comparison of the two groups evaluated based on TINETTI gaitand balance test.

TINETTI Balance	Interventions (n=25)	Control (n=25)	T	p
Baseline				
Min.–Max.	11.0– 16.0	11.0– 16.0	0.486	**0.629**
Mean±SD.	13.20± 1.63	13.44± 1.85		
Median(IQR)	13.0(12.0 –14.0)	14.0(12.0–15.0)		
After 6 weeks				
Min.–Max.	14.0– 27.0	11.0– 15.0	3.829*	**<0.001***
Mean±SD.	16.64± 4.01	13.32± 1.65		
Median(IQR)	15.0(15.0–16.0)	14.0(12.0–15.0)		
t(p_0)	**5.897* (<0.001*)**	**0.681(0.503)**		

Table5. Comparison between the two studied groups according to Gait

Gait	Interventions (n=25)	Control (n=25)	T	p
Baseline				
Min.–Max.	20.0– 24.0	20.0– 24.0	0.328	**0.744**
Mean±SD.	22.24± 1.13	22.36± 1.44		
Median(IQR)	23.0(21.0–23.0)	22.0(21.0 –24.0)		
After 6 weeks				
Min.–Max.	23.0– 29.0	21.0– 25.0	6.899*	**<0.001***
Mean±SD.	26.12± 1.81	23.04± 1.31		
Median(IQR)	26.0(25.0–28.0)	23.0(22.0–24.0)		
t_0(p_0)	**9.874* (<0.001*)**	**7.141* (<0.001*)**		

Table 6. Comparison between the two studied groups according to the modified Toronto clinical neuropathy score

Clinical neuropathy score	Interventions (n=25)	Control (n=25)	T	p
Baseline				
Min.–Max.	9.0 –13.0	9.0 –14.0	0.276	**0.783**
Mean±SD.	11.28± 1.46	11.40± 1.61		
Median(IQR)	11.0(10.0–13.0)	12.0(10.0–12.0)		
After 6 weeks				
Min.–Max.	7.0 –11.0	9.0 –13.0	4.381	**<0.001***
Mean±SD.	9.32± 1.11	10.88± 1.39		
Median(IQR)	10.0(9.0– 10.0)	11.0(10.0–12.0)		
$t_0(p_0)$	**12.413* (<0.001*)**	**5.099* (<0.001*)**		

Table 7. Ananalysis of the two groups under study reveals the differences and similarities between them based on NIS-L

NIS-L	Interventions (n=25)	Control (n=25)	T	p
Baseline				
Min.–Max.	5.0 –8.0	5.0 –8.0	0.628	**0.533**
Mean±SD.	6.92± 1.0	6.72± 1.24		
Median(IQR)	7.0(6.0–8.0)	7.0(5.0–8.0)		
After 6 weeks				
Min.–Max.	3.0 –6.0	5.0 –9.0	5.898	**<0.001***
Mean±SD.	5.24± 0.97	7.08± 1.22		
Median(IQR)	6.0(5.0–6.0)	7.0(6.0–8.0)		
$t_0(p_0)$	**12.167* (<0.001*)**	**3.674* (0.001*)**		

Table 8. An analysis of the two groups under study in relation to quality of life

Parkinson's disease quality of life score	Interventions (n = 25)	Control (n=25)	T	P
Baseline				
Min.–Max.	21.0– 26.0	21.0– 27.0	0.336	**0.738**
Mean±SD.	23.64± 1.52	23.80± 1.83		
Median(IQR)	23.0(23.0–25.0)	24.0(22.0–25.0)		
After 6 weeks				
Min.–Max.	20.0– 25.0	24.0– 27.0	13.219*	**<0.001***
Mean±SD.	22.16± 1.03	25.56± 0.77		
Median(IQR)	22.0(21.0–23.0)	26.0(25.0–26.0)		
t_0 (p_0)	**7.472* (<0.001*)**	**4.342* (<0.001*)**		

Table 9. Comparison between the two studied groups according to BDI score

BDI score	Interventions (n=25)	Control (n=25)	T	P
Baseline				
Min.–Max.	10.0– 16.0	10.0– 16.0	0.777	**0.441**
Mean±SD.	13.28± 1.65	12.92± 1.63		
Median(IQR)	13.0(12.0–15.0)	13.0(12.0–14.0)		
After 6 weeks				
Min.–Max.	7.0 –12.0	10.0– 15.0	6.943*	**<0.001***
Mean±SD.	9.92± 1.38	12.76± 1.51		
Median(IQR)	10.0(9.0– 11.0)	12.0(12.0–14.0)		
$t_0(p_0)$	**18.515* (<0.001*)**	**1.072 (0.294)**		

Table 10. Comparison between the two studied groups according to BDNF

BDNF	Interventions (n=25)	Control (n=25)	T	P
Baseline				
Min.–Max.	20.0– 30.0	21.0– 29.0	0.351	**0.727**
Mean±SD.	25.28± 3.05	25.0± 2.57		
Median(IQR)	25.0(23.0–28.0)	25.0(22.0–27.0)		
After 6 weeks				
Min.–Max.	36.0– 95.0	21.0– 28.0	9.781*	**<0.001***
Mean±SD.	63.48± 19.78	24.52± 2.33		
Median(IQR)	65.0(45.0–80.0)	24.0(22.0–27.0)		
$t_0(p_0)$	**10.417* (<0.001*)**	**3.674* (0.001*)**		

Table 11. An analysis of the two groups was conducted to compare their levels of folic acid and vitamin B12.

	Interventions (n=25)	Control (n=25)	T	P
Folic acid				
Min.–Max.	7.0 –12.0	12.0– 19.0	10.135*	**<0.001***
Mean±SD.	9.56± 1.61	15.08± 2.20		
Median(IQR)	10.0(8.0– 10.0)	15.0(13.0–16.0)		
VitaminB12				
Min.–Max.	327.0– 543.0	458.0– 768.0	6.475*	**<0.001***
Mean±SD.	400.2± 64.96	569.6± 113.6		
Median(IQR)	**387.0(342.0–423.0)**	**546.0(468.0–654.0)**		

Table 12. An analysis was conducted to compare the two groups under study based on their diastolic blood pressure (DBP) and systolic blood pressure (SBP).

	Interventions (n =25)		Control (n=25)		Test of Sig.	P
Circadian BP rhythm	**No.**	**%**	**No.**	**%**		
Nondipping	6	24.0	14	56.0	χ^2=7.929	$^{MC}p=$ 0.019
Dipping	2	8.0	4	16.0		
Reverse dipping	17	68.0	7	28.0		
DBP24-h						
Min.–Max	69.0– 79.0		63.0– 79.0		t=2.073	0.60
Mean±SD.	71.51± 7.1		70.95±8.13			
Median(IQR)	74.0(70.0–78.0)		73.0(68.0–76.0)			
SBP24-h						
Min.–Max.	127.0– 140.0		125.0– 138.0		t= 0.140	0.889
Mean±SD.	132.60±4.08		132.44±3.99			
Median(IQR)	**132.0 (128.0–136.0)**		**133.0 (130.0–135.0)**			

Table 13. Comparison of the two groups under study based on many parameters in 24h Holter monitoring

	Interventions (n=25)	Control (n=25)	t	P
SDNN				
Min.–Max.	87.00– 122.0	127.0– 160.0	12.899*	<0.001*
Mean±SD.	102.2± 12.52	144.1± 10.36		
Median(IQR)	100.0(87.0–114.0)	142.0(134.0–154.0)		
SDANN				
Min.–Max.	87.0– 108.0	106.0– 140.0	12.169*	<0.001*
Mean±SD.	92.64± 6.24	120.2± 9.45		
Median(IQR)	90.0(87.0–96.0)	123.0(112.0–126.0)		
RMSSD				
Min.–Max.	25.0– 40.0	35.0– 68.0	10.818*	<0.001*
Mean±SD.	33.08± 4.03	53.16± 8.36		
Median(IQR)	32.0(32.0–36.0)	53.0(52.0–56.0)		
NN				
Min.–Max.	3214.0–3956.0	5896.0–7423.0	27.052*	<0.001*
Mean±SD.	3519.0±246.3	6428.7±478.1		
Median(IQR)	3526.0(3245–3695)	6352.0(5986–6541)		
PNN50				
Min.–Max.	2.90– 3.90	6.30– 8.0	30.003*	<0.001*
Mean±SD.	3.37± 0.37	7.41± 0.56		
Median(IQR)	**3.30(3.0– 3.80)**	**7.50(7.20 –7.90)**		

Table 14. An analysis was conducted to compare the two groups that were studied based on their TI, DI, and LI.

	Interventions(n=25)	Control (n=25)	t	P
TI				
Min.–Max.	22.0– 30.0	32.0– 39.0	14.413*	<0.001*
Mean±SD.	25.32± 2.39	34.96± 2.34		
Median(IQR)	25.0(24.0–26.0)	35.0(33.0–36.0)		
DI				
Min.–Max.	59.0– 69.0	79.0– 90.0	23.475*	<0.001*
Mean±SD.	62.92± 2.75	85.24± 3.88		
Median(IQR)	62.0(62.0–65.0)	85.0(80.0–89.0)		
LI				
Min.–Max.	60.0– 69.0	41.0– 48.0	29.089*	<0.001*
Mean±SD.	63.36± 2.50	44.0± 2.20		
Median(IQR)	**63.0(62.0–65.0)**	**44.0(42.0–45.0)**		

DISCUSSION

Regarding motor nerve conduction velocity (NCV) in the ankle fibular head, fibular head-popliteal fossa, and tibial nerve, the two groups did not differ significantly from one an other. initially. However, after 6 weeks, there was a substantial improvement in the interventional group compared to the control group .Regarding the clinical neuropathy score, there were no significant differences between the two groups at the beginning of the study. However, after 6 weeks, the interventional group showed a substantial improvement in comparable to the control group.

Regarding the NIS L score, there were no significant changes between the two groups at the beginning. However, after 6 weeks, there was a substantial improvement in the interventional group compared to the control group.

A study examining the possible advantages of physical activity in individuals with PD determined that exercise has the ability to enhance physical performance, overall health and well-being, leg muscle strength, balance, posture, walking ability, and fitness levels [11].

Hence, the authors' assertion on the enhancement of functional motor performance in patients with Parkinson's disease by exercise seems strong. Nevertheless, the issue of determining the most suitable exercise regimen for each individual patient remains unresolved [12].

The presence of enhanced motor and cognitive behavioral abilities, along by corresponding alterations at the brain level and adecrease in periods of diminished functionality, indicates that exercise may have a neuro protective effect on Parkinson's patients. AE enhances the functionality and organisation of CNS. [13] And preserved decline of white matter pathways associated with ageing [14].

Regarding TINETTI, there were no significant changes between the two groups at the beginning. However, after 6 weeks, there was a notable improvement in the interventional group compared to the control group.

In contrast to the findings of Cheng et al. [15], it was seen that the group assigned to the specific training regimen out performed the control group in various aspects. These included the TINETTI balance scale, the limit of stability test, as well as the strength of the lower extremities extensor sand abductors. The training groups that utilized a turning-based approach exhibited superior performance compared to the control group in terms of sensory organisation and ankle plantar flexor strength. To summaries, both targeted exercise training and interval-based treadmill training were successful in enhancing turning ability in individuals with Parkinson's disease (PD).

Nevertheless, the enhancements in manoeu vrability exhibited by these two cohorts were a consequence of addressing distinct facets of debilitation in persons diagnosed with Parkinson's disease [14].

Initially, there were no notable alterations in gait between the two groups. After a duration of 6 weeks, the interventional group exhibited a significant improvement in comparison to the control group.

According to two studies [16,17],75% of the comparison group demonstrated improvements after receiving AE treatment. The AE (AE) was performed on a treadmill, and the duration of the protocols ranged from four to 24 weeks.

While AE has shown the ability to enhance gait speed, finding interventions that can improve spatiotemporal gait characteristics, freezing of gait, and dual task execution remains a challenging job. Additionally, a reduced walking pace is

linked to an increased likelihood of falls and problems in people with Parkinson's disease [18]. This highlights the significance of rehabilitative programs that specifically address this issue.

At the onset of the trial, there were no notable disparities in the quality of life score between the two groups. Nevertheless, after a duration of 6 weeks, the interventional group shown a significant enhancement in comparison to the control group.

With respect to quality of life, the available evidence was of a significantly low level and did not demonstrate any impact. Only a single study [19] reported a 16.7% improvement in the comparison group following the intervention with AE. There is no evidence to suggest that either short- or long-duration AE (lasting from six to 24 weeks) can enhance self-reported quality of life, regardless of whether the exercise is performed on a treadmill or through walking. The sole study of Arfa-Fatollah khani et al. [19] that shown enhancement following AE therapy utilized the 8-ItemShort-FormHealth Survey evaluation tool, a condensed iteration of the 36-Item Short-Form Health Survey (SF-36).

The SF-36 has two categories, namely physical and mental. TheSF-36, a shortened version of the questionnaire used to measure quality of life, has been employed to evaluate the impact of treatments on individuals with PD. Studies using the 12-Item Short-Form Health Survey have shown a notable improvement in this aspect, such as when investigating the effects of robot-assisted aerobic training in this population [20].

In contrast, the PDQ-39 was utilized in the majority of investigation sand did not show any notable enhancement following the intervention with AE.

Nevertheless, one study [21] observed a significant enhancement in domain six, which pertains to the assessment of cognitive function in persons with PD, following treatment.

According to Lawson et al. [22], patients with PD had improvements in their ability to focus, remember, and retrieve information following the intervention. This could potentially have a beneficial effect on their overall quality of life.

Regarding the BDI score, there were no significant differences between the two groups at the beginning of the study. However, after 6 weeks, there was a substantial improvement in the interventional group compared to the control group.

Exercise can be just as advantageous as medical treatments or cognitive behavioral therapy in treating depression in those with chronic conditions.

Meta-analyses of quasi-experimental studies and randomized controlled trials (RCTs) investigating the use of exercise for controlling depression in PD have yielded inconclusivefindings.

Whileseveralstudieshavedemonstratedareductionindepressivesymptoms,othershave showed no significant effect [23]. One possible reason for these contradictory findings is the variation in study methodology, including differences in the tools used to measure depression outcomes (such as the BDI, Hospital Anxiety and Depression Scale, Hamilton Rating Scale of Depression, Montgomery-Asperg Depression Rating Scale, The Geriatric Depression Scale, and Beck Anxiety Inventory) and the type of exercise intervention implemented.

De Lima et al. [24] examined the antidepressant impact of resistance training in persons diagnosed with PD. The study utilized the 17-item Hamilton Depression Rating Scale to measure the depressive symptoms of participants in the resistance training exercise group.

These individuals engaged in 20 to 40 minutes of training, twice a week, for a duration of 20 weeks. The results showed a significant decrease in depressive symptoms, as well as an improvement in the quality of life (QOL) measured by "The 39-item Parkinson's Disease Questionnaire" (PDQ-39), and decrease in parkinsonism measured by the total score of

"The Unified Parkinson's Disease Rating Scale" (UPDRS). Conversely, the control group did not experience any improvement in QOL, or UPDRS scores or depressive symptoms after the 20-week period [24].

Regarding the "Brain-derived neurotrophic factor" (BDNF), Initially, there were no substantial distinctions between the two groups. However, after 6 weeks, there was a notable improvement in the interventional group compared to the control group.

Furthermore, a comprehensive analysis demonstrated that the data collected from four pre-experimental investigations and two randomized controlled trials and, involving a total of 100 ambulatory patients with idiopathic Parkinson's disease (Hoehn/Yahr $\leq$3), revealed that all six studies (two RCTs and four pre- experimental studies) demonstrated improvements in blood concentration levels of BDNF.

The pooled change scores of BDNF levels from the two randomized controlled trials (RCTs) showed a substantial and consistent summary effect size (Standardised Mean Difference 2.06, 95% CI 1.36 to 2.76). Additionally, there was a significant and varied impact size for the motor section of the UPDRS-III test (MD -5.53, 95% CI -10.42 to - 0.64). All investigations observed positive clinical advancements across various outcome measures [7].

Research involving psychiatric disorders has found that non pharmacological interventions, such as exercise, can lead to clinical improvements by increasing levels of serum BDNF [25,26].

Additionally, we observed a noteworthy reduction in the interventional group compared to the control group in terms of folic acid and Vitamin B12 levels.

Consistent with our findings, Triantafyllou NI et al discovered that Parkinson's disease (PD) patients who were treated withLevodopahadnotablylowerlevelsoffolateandvitaminB12intheirbloodcomparedtoindividuals without neurological conditions. Additionally, depressed patients exhibited significantly lower levels of serum folate compared to those who were not depressed [27].

The present investigation found a notable disparity between the two groups in terms of 24-hour blood pressure and heart rate variability.

Similarly, Heimrich et al. [28] conducted a comprehensive analysis that encompassed 47 research including a total of 2772 individuals. Random-effects meta-analyses demonstrated a substantial reduction in effect sizes among PD's patients, both the HFms2 component of the spectrum and the RMSSD measurement over the near term.

Nevertheless, there was a significant level of diversity, and there were indications of biased publication in relation to HFms2. Research conducted by Heimrich et al. [28] suggests that an advanced disease may result in a compromised parasympathetic control.

CONCLUSION

AE effectively enhanced motor NCV in the Ankle fibular head, Fibular head– popliteal fossa, and Tibias nerve. It also improved sensory NCV, TINETTI, gait, clinical neuropathy score, NIS L score, BDNF, quality of life score, and BDI score.

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