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Research Article
Clinical Prediction Rules for Using Aerobic Exercises on Executive Functions in Parkinson's Patients

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Abstract

Background and Objective: Impaired executive function can adversely affect motor performance and is closely related to fall risk in parkinson's patients. Aerobic exercise improves executive function and prevent falling in healthy older adults. The aim of this study was to investigate the predictors for using aerobic exercise to improve executive functions and decrease fall in parkinson patients. **Materials and Methods:** About 36 idiopathic recurrent faller parkinson's patients treated by aerobic treadmill exercise for two months day after day each session 30 min. They assessed by screening part of rehacom, up and go test, faller diary pre and post-treatment. **Results:** There was no significant difference in mean value of age between the successful and unsuccessful group ($p = 0.0758$). Patients in the successful group were significantly ($p = 0.0130$) less severe (2.15 ± 0.881) than patients in the unsuccessful group (3.20 ± 1.033). Patients in the successful group had significantly ($p = 0.0012$) shorter (less) disease duration (3.88 ± 2.304 year) than patients in the unsuccessful group (7.200 ± 3.084 year). According to receiver operator characteristic ROC curve, the cutoff point for severity of illness was 4, the cutoff point for duration of illness was 5 years. In the successful group there were significant difference between TUG-Pre and TUG-Post ($p = 0.0001$), dairy-pre and dairy-post ($p = 0.0001$) and rehacom-pre and rehacom-post ($p = 0.0001$). **Conclusion:** Duration and severity of illness are considered significant predictors for the use of aerobic exercises for improving the executive functions in PD patients. Improvement of executive functions is significantly correlated with improving the risk of falling in patients with PD.

Key words: Aerobic exercise, clinical prediction rules, treadmill exercise, executive functions, rehacom, ROC curve

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Motor deficits are greatly focused during different physical therapy interventions for patients with parkinson disease (PD). Impaired cognition is considered one of the most important factors that affect the management of the motor deficits associated with PD and the overall wellness of the individual. Cognition is highly affected in PD patients[1].

Aerobic exercises improve executive function and prevent deterioration of attention, abstraction, visual construction, judgment, verbal fluency and immediate or delayed verbal recall in PD patients individuals with pre-existing neurological, psychiatric and cognitive impairments may also be improved by exercise[1].

Cognition includes multiple mental processes such as executive functions. Executive functions are not limited to judgment, planning, initiation, abstraction, problem solving, sequencing and mental flexibility. Individuals with PD suffer from impaired executive function[2].

The incidence of mildly impaired executive function in people with PD has been reported to be as high as 44%, with the incidence of PD dementia of 29%. Impaired executive function is reported to be a great indicator for the quality of life in PD patients. Motor performance can be greatly affected by impaired executive function resulting in increase the risk of fall in individuals with PD[3].

Up to 68% of people with Parkinson's disease will fall and 46% of people with parkinson's disease will experience falls recurrence each year. These rates are double of those in the general older population. In addition, a 12 month prospective study (n = 113) found that 27% of individuals with parkinson's disease fell at least once each month and 15% fell at least once a week[4].

Among parkinson disease individuals, 65% of patients will experience an injury secondary to their falls, 33% will suffer a fracture and 75% of falls will result in use of a health care service. Falls and related fractures are the most common secondary causes of parkinson's disease patients' hospital admission. Pain, reduced mobility and unacceptably high levels of care giver stress are accompanied with parkinson's falls[4].

History of falls, postural instability, freezing of gait, leg muscle weakness and cognitive impairment are the main risk factors causing falls in people with PD. There a falls has wide variation among PD patients. single falls may have different risk factors from the recurrent falls[5].

Clinical prediction rules (CPRs) are algorithmic decision tools designed to aid clinicians in determining a diagnosis, prognosis or likely response to an intervention. They use a parsimonious set of clinical findings can be collected through the history, physical examination and diagnostic test results that have been analyzed and found to be statistically meaningful predictors of a condition or outcome of interest[6]. RehaCom is a comprehensive and sophisticated system of procedures for computer-assisted cognitive assessment and rehabilitation. Physical therapist can use this practical tool in the assessment and rehabilitation of cognitive disorders which affect attention and concentration, figural memory, reaction behavior and logical reasoning[7].

As study reported that impaired executive function which is the main cause for falling in parkinson's due to impaired motor performance can be highly improved by aerobic exercises without reporting the predictors for its use. So, the aim of the present study was to investigate the predictors for using aerobic exercise to improve executive functions and decrease fall in parkinson patients and also was designed to determine the correlations between the executive functions and recurrent fall.

MATERIALS AND METHODS

The current study was done to assess and investigate which predictor variables were associated with favorable treatment response of aerobic exercise on executive function in parkinson patients and also to determine the correlation between executive function and recurrent fall.

Thirty six Levodopa dependent PD patients were allocated in the current study. They were selected from Huda Talat Harb hospital for geriatric rehabilitation. The patients were diagnosed and referred by a neurologist. Computed Tomography (CT) scan was used to exclude any other neurological conditions that may affect gait, balance or cognition. The clinical predictor variables suggested were the age, the duration of illness and the severity of the disease according to Hoehn and yahr scale.

All patients were subjected to complete clinical assessment (including careful history taking, duration of illness, motor, sensory, co-ordination, activity of daily living and gait assessment). Geriatric Depression Scale (GDS) was used before treatment for the detection of the presence of depression. Patients with score $\geq$12 were excluded. Cognitive function was assessed by MOCA scale. Patients with score less than 26 were included in the study. Timed up and go test was used to assess stability and it was done before and after treatment. Falling diary was also completed by asking the patient to record in his diary the numbers of falling in the next two months following the treatment then falling numbers were recorded through a phone call.

The treatment program included aerobic exercise in the form of treadmill training. In the 1st week, patients walked on treadmill till tolerance at 40-50% max HR and then progressed to the 70% max HR in the 2nd week. Intensity of aerobic exercise was systematically progressed for each patient by increasing speed to maintain conditioning at 70% max HR.

Maximum heart rate calculated from the following equation (max HR = 220-age). The first 5 min of each session were dedicated to warming up exercise on the treadmill in the form of slow progression exercise (to decrease the risk of hypotension, musculoskeletal injury and cardiovascular complications), followed by the active phase of exercise for 20 min and finally cooling down phase for 5 min, with intensity and speed decreased gradually until reaching the resting heart rate (RHR).

Statistical analysis: The statistical analysis was conducted by using statistical SPSS Package program version 20 for windows (SPSS, Inc., Chicago, IL). Descriptive statistics including the mean and standard deviation for age, severity of illness, duration of illness, timed up and go test, dairy and rehacom score.

Paired t-student test to compare between pre and post-treatment within successful and unsuccessful groups. Unpaired (Independent) t-student test to compare between successful and unsuccessful groups for age and timed up and go test (TUG). Wilcoxon-test was used to compare between pre- and post-treatment for severity of illness, duration of illness and diary within successful and unsuccessful groups. Mann-Whitney-test to compare between post-treatment for severity of illness, duration of illness and diary successful and unsuccessful groups. Sensitivity, specificity and cutoff point values were calculated and plotted as receiver operator characteristic (ROC). Spearman rank correlations to calculate correlation coefficients (r) between rehacom score with mean value of diary and TUG test in successful group. All statistical analyses were significant at 0.05 level of probability ($p \leq 0.05$).

RESULTS

Thirty six patients completed the treatment and assessment procedures (4 patients drop out = 10%) as shown in Table 1. Twenty two male and 14 female participated in the study, 13.9% stage (1), 25% stage (1.5), 19.44% stage (2), 8.33% stage (2.5), 8.33 % stage (3) and 25 % stage (4) according to Modified Hoehn and Yahr staging of Parkinson's severity.

There was no significant difference ($p = 0.0758$) between the two groups. Patients in the successful group were significantly ($p = 0.0130$) less severe (2.15 ± 0.881) than patients in the unsuccessful group (3.20 ± 1.033) as shown in Table 2.

For duration of illness, patients in the successful group had significantly ($p = 0.0012$) shorter (less) disease duration than patients in the unsuccessful group as shown in Table 3.

According to ROC curve, the cutoff point for severity of illness was 4. This means patients less severe than grade 4 at Modified Hoehn and Yahr scale are more likely to benefit from the prescribed aerobic exercise program in improvement of executive function.

According to ROC curve, the cutoff point for duration of illness was 5 years. This means patients with duration of illness less than 5 years are more likely to benefit from the prescribed aerobic exercise program in improvement of executive function as shown in Table 4.

In the successful group, There were significant difference between TUG- Pre and TUG- Post ($p = 0.0001$), dairy-pre and dairy-Post ($p = 0.0001$) and rehacom-pre and rehacom-post ($p = 0.0001$).

In the unsuccessful group, there were no significant difference between TUG-Pre and TUG- Post ($p = 0.8572$) and dairy-pre and dairy-post ($p = 0.1934$). While, there was significant difference between Rehacom-pre and rehacom-post ($p = 0.047$) as shown in Table 5.

Table 1: Age in the successful and unsuccessful groups (Mean±SD)

Treatment groups	n	Mean	Standard deviation
Patient groups	36	69.14	8.103
Successful group	26	67.65	8.265
Unsuccessful group	10	73.00	6.532

					95% CI of the difference	
Treatment groups	Successful	Unsuccessful	Mean difference	p-value	Lower	Upper
Age (years)	67.65±8.265	73.00±6.532	5.346±2.919	0.0758	-11.278	0.585

Significant ($p<0.05$), CI: 95% confidence interval

Table 2: Severity of illness in the successful and unsuccessful groups (Mean±SD)

Treatment groups	Successful (Mean±SD)	Unsuccessful (Mean±SD)	Mean difference	p-value	95% CI of the difference Lower	Upper
Severity of illness	2.15±0.881	3.20±1.033	1.046±0.369	0.0130	-1.837	-0.255

Table 3: Duration of illness, TUG-Pre (sec) and diary-pre in the successful and unsuccessful groups (Mean±SD)

Treatment groups	Successful (Mean±SD)	Unsuccessful (Mean±SD)	Mean difference	p-value	95% CI of the difference Lower	Upper
Duration of illness	3.880±2.304	7.200±3.084	3.320±0.9349	0.0012	-5.231	-1.399
TUG	21.460±4.810	31.500±5.701	10.040±1.8830	0.0001*	-13.866	-6.211
Diary	1.615±0.5711	1.900±0.3162	0.285±0.1920	=0.1140	-0.592	0.022

Table 4: Cutoff point for severity and duration of illness

Predictor	Sensitivity	Specificity	+LR	-LR	Cutoff
Severity of illness	0.885 (0.7-0.967)	0.6 (0.312-0.831)	2.212	0.192	4
Duration of illness	0.731 (0.536-0.864)	0.800 (0.478-0.951)	3.654	0.337	5

Table 5: Pre- and Post-TUG, diary and rehacom score within successful and unsuccessful groups (Mean±SD)

	Successful groups			Unsuccessful groups		
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Variables	Mean±SD	Mean±SD	p-value	Mean±SD	Mean±SD	p-value
TUG (sec)	21.46±4.810	16.88±4.918	0.0001*	31.500±5.7010	31.200±8.9290	0.8572
Diary	1.62±0.571	0.50±0.583	0.0001*	1.900±0.3162	1.600±0.6992	0.1934
Rehacom	11.23±2.854	29.42±8.093	0.0001*	17.290±7.0780	13.380±2.2300	0.0520

Table 6: Post-TUG, diary and rehacom score between successful and unsuccessful groups (Mean±SD)

	Post treatments		
Variables	Successful group Mean±SD	Unsuccessful group Mean±SD	p-value
TUG (sec)	16.88±4.918	31.20±8.9290	0.0001*
Diary	0.50±0.583	1.60±0.6992	0.0001*
Rehacom	29.42±8.093	13.38±3.1220	0.0078*

Table 7: Correlation between post-treatment changes in the mean value of Rehacom score and changes in the mean value of diary and TUG test in successful group

Parameters	r	p-value
Diary	-0.5126	0.0074*
TUG test	-0.3885	0.0498*

Table 8: Correlation between post-treatment mean value of Rehacom score and mean value of diary and TUG test in successful group

Parameters	r	p-value
Diary	-0.4049	0.0377*
TUG test	-0.4315	0.0277*

There were significant difference between TUG-Post (p = 0.0001), dairy-post (p = 0.0001) and rehacom-post (p = 0.0001) between successful and unsuccessful groups as shown in Table 6.

The results indicated that there was a significant negative correlation between improvement in Rehacom score and decrease in mean value of diary and TUG test in successful group (p = 0.0074 and 0.0498, respectively). This means that improvement in cognitive function is consistent with improvement in stability, decrease risk of fall as shown in Table 7.

The results indicated that there was a significant negative correlation between improvement in Rehacom score and decrease in mean value of diary and TUG test in successful group (p = 0.0377 and 0.0277, respectively). This means that improvement in cognitive function is consistent with improvement in stability , decrease risk of fall as shown in Table 8.

DISCUSSION

The results of the current study reported that the duration of illness and severity of disease may be considered as important predictor variables associated with favorable treatment response of aerobic exercise on executive function in parkinson patients while the age doesn't affect the

response of aerobic exercise on executive function. It was also found that there is a strong correlation between executive function and falling.

The results of the present study revealed significant improvement in executive functions in parkinson's patients. This improvement may be attributed to the physiological effects of aerobic physical exercise (PE). Exercises can activate the release of neurotrophic factors and promotes angiogenesis, thereby facilitating neurogenesis and synaptogenesis, which in turn improve memory and cognitive functions. The neuroprotective mechanisms induced by PE are related to increased production of superoxide dismutase, endothelial nitric oxide synthase, brain-derived neurotrophic factor, nerve growth factor, insulin-like growth factor, vascular endothelial growth factor and reduction of the production of free radicals in brain areas such as the hippocampus, which its main function is memory. Exercise limits the alteration in dopaminergic neurons in the substantia nigra which acts as a key neurotransmitter in the brain and to large extent responsible for improving the cognitive deficits[8].

Also these results may attributed to the effects of aerobic exercise on improving cardiorespiratory fitness level which has been associated with a reduced age-related loss of grey and white matter in the frontal, prefrontal and temporal regions in older adults, whereas the caudate nucleus volume has been thought to mediate the relationship between the level of cardiorespiratory fitness and task switching performance in older healthy adults[9,10].

The results of the present study contradicted with the finding of Ploughman *et al.*[11], who reported that treadmill exercise did not cause improvement in cognitive function (including the Trail Making Test A and B, Symbol Digit Substitution Test and Paced Auditory Serial). The discrepancy between the present and Ploughman *et al.*[11] study may be attributed to the small sample size and the short duration of the physical therapy. It was assumed that sustained aerobic exercise (over months) is required for cognitive improvement[12].

The current study revealed also that improvement of executive functions is associated with improved postural stability and decrease fall risk in Parkinson this may be explained by that the response inhibition is one component of executive function which is an important factor in adaptation to the changing environment that occurs in daily life. There is evidence of an association between impairment of response inhibition and slower responses to distracter stimuli and poorer balance and gait performance and increased falls in older people. It is important component as it would allow people to focus on maintaining balance during walking by ignoring concurrent distractions from the environments[13,14].

Correlation between executive functions and postural stability and falling may be caused by poorer performance of executive function which was associated with decreases in velocity, temporal (longer stride time) and spatial parameters (shorter stride length) of gait for the participants with PD in comparison to healthy subjects. Theses results can be explained by that the PFC and subcortical areas may affect gait speed in older adults and these regions are highly related to executive function. Importantly, the association between deficits in executive function, balance and gait abnormalities may be caused by white matter abnormalities resulting in affection of the connectivity of networks between the basal ganglia and the frontal cortex (fronto-striatal circuits). These circuits are responsible for regulating both motor and cognitive function. The disruption of subcortical white matter has been reported to be associated with deterioration of cognitive function and mobility in people with PD. Defective basal ganglia circuits in PD patients may impair balance and postural stability[15-24].

The results of the current study reported that the severity of disease and duration of illness are predictors for favorable response for aerobic exercise on executive functions in parkinson's patients. The patients in the successful group were significantly less severe and shorter duration than patients in unsuccessful group.

Patient in moderate stages of the disease showed deficits in some parameters of executive functions. Lower performance was observed for abstraction and mental flexibility in patients in moderate stage of DP than in patients in early stage of the disease. Cognitive impairment, especially in executive functions deteriorate more with the disease progression[25]. Patients in the moderate stages of the disease scored significantly lower for mental flexibility and abstraction capacity when compared to the early stages of the disease. The drastic decrease of dopaminergic neurons in the late stages of PD can cause a decrease in the response of neuroplasticity to exercise. The exercise effects are more obvious in patients with early stages of the disease[26].

Disease duration and pain can adversely affect exercise participation in people with PD[27]. About 80% of dopaminergic cells are already damaged with the first symptoms of PD, which gradually worsens with disease progression[28]. The dopaminergic neurons are highly responsive to exercise[29]. With the first diagnosis of PD, only 30% or so of dopamine

neurons of the SN have been lost and only 50-60% of their axon terminals. There is, therefore; a substantial window of chance for preservation. Both the mechanisms of axon degeneration and the potential for axon regrowth in the mature central nervous system are better at very early stages[30].

CONCLUSION

The current study demonstrated that the duration and severity of illness are considered significant predictors for the use of aerobic exercises for improving the executive functions in PD patients. Improvement of executive functions is significantly correlated with improving the risk of falling in patients with PD.

IMPLICATIONS

- This study will improve decision making concerning using aerobic exercise for improving executive functions and decrease fall in Parkinson patients and in physical therapy field it help to assisting practitioners matching patients to optimal interventions based on a parsimonious subset of predictor variables from the history and physical examination

APPLICATIONS

- From the clinical examinations and history of patients therapist can choose the best intervention
- Improving cognition functions to improve motor functions and decrease falling risk

RECOMMENDATIONS AND LIMITATIONS OF THE STUDY

- The authors recommend to perform the same study but with larger number of patients
- Study other predictors effect on of aerobic exercise on executive functions as site of lesion, education level, sex⋯etc
- Study the correlation of improvement of executive functions on Parkinson patient's quality of life
- The limitations of the present study were mostly due to the difference in the psycho-physiological status of the patients at the time of assessment and also due to small sample size

SIGNIFICANT STATEMENT

This study will improve decision making concerning using aerobic exercise for improve executive functions in Parkinson's patients and in physical therapy field helps to assist practitioners to matching patients to optimal interventions based on parsimonious subset of predictor variables from the history and physical examination. Improving executive functions and decrease fall risk very important to improve Parkinson's patients quality of life.

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