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Effect of Non-Invasive Cranial Stimulation on Motor and Cognitive domains in Individual with Parkinson's disease: A Pilot Study

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ABSTRACT
Parkinson's disease is a chronic, progressive neurodegenerative condition characterized by the degeneration of dopaminergic neurons within the basal ganglia, resulting in both motor and cognitive deficits. In recent years, non-invasive brain stimulation methods such as Repetitive Transcranial Magnetic Stimulation (rTMS) have gained attention in rehabilitation for their potential to support functional recovery. The present study investigated the effects of rTMS on motor and cognitive functions in individuals with Parkinson's disease. Ethical approval was obtained from Punjabi University, Patiala (Ref. No. 26/55/IEC/PUP/2022). A total of ten participants, aged between 50 and 75 years with a confirmed diagnosis of Parkinson's disease (Hoehn and Yahr stages I–III) and cognitive impairment were enrolled. Individuals with other neurological conditions, metallic implants or brain tumors were excluded. The intervention involved rTMS applied to the supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC) for 20 minutes daily over a period of 15 days combined with conventional physiotherapy. Assessments included the MDS-UPDRS III, MoCA, Disability Rating Scale (DRS) and PD-QOL. Findings revealed improvements across all measured domains, indicating that rTMS may be effective in enhancing both motor and cognitive performance in Parkinson's disease.

INTRODUCTION:

Parkinson's disease was firstly described by Dr. James Parkinson's as Shaking palsy in year 1817 [16]. It is a chronic progressive neurodegenerative disorder of movement characterised by pathological changes results in loss of dopaminergic neuron in substantia nigra which causes an abnormal activity in striatal-thalamic cortical pathway[3,4]. It is progressively growing long term age related degenerative disorder of central nervous system which induces dysfunction in the extrapyramidal motor system associated with the functional loss of dopaminergic nigrostriatal function. After Alzheimer's disease Parkinsons disease is recognised as one of the most common neurological disorders affecting approximately 1% of individual older than 60 years [22]. The incidence and prevalence of Parkinson's disease is increasing yearly & commonly early onset is before the age of 40 years which account for 3-5 of cases and commonly occurs in males [20]. Most incidences studies have been performed in Europe, with overall incidence rates between 9 and 22 per 100,000 individuals per year[24]. The overall prevalence of 42.3 per 10,000 of PD and prevalence over age of 60 was 308.9 per 100000 which is increasing with advancing age. The 60–70-year-old age group has high risk of developing Parkinsons disease[17]. In Northern India Prevalence effected by PD is 67.71/105 effected. In

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Mumbai 328 per 10,0000 population effected by PD[18].

Among the motor and non-motor symptoms, the individual with Parkinson disease commonly experiences motor impairment and cognitive impairments. The motor impairment is linked with the subsequent loss of dopamine in basal ganglia, causes the over activity of the internal global pallidus resulted in the inhibition of thalamus to activate the frontal cortex [7]. The motor impairment mainly interferes with gait [16]. Cognitive impairment is now recognised as a common non-motor symptom of Parkinson's disease. Increasingly, changes in neurotransmitter systems beyond dopamine, including the noradrenergic, serotonergic and cholinergic systems, are being recognized for their contribution to cognitive decline. In comparison with healthy controls, PD patients show a substantial decline in a wide range of cognitive domains, predominantly in executive functions, attention and visuospatial abilities [10].

The aim of maximizing the recovery rate the advanced rehabilitation methods were proposed such as non-invasive brain stimulation[12]. Therefore, in recent years based on reporting guidelines founded by a group of European experts on the therapeutic application of Repetitive Transcranial Magnetic Stimulation (rTMS) recommended as potential tool for therapeutic tool for various neurological and psychiatric disease[13]. rTMS is the form of neuromodulation non-invasive brain stimulation which is pain-free and used to improve the cortical performance which induce currents in local areas of cerebral cortex by changing magnetic fields to depolarize nerve cells of central nervous system and produce activity of synaptic terminals which can lead to number of metabolic changes in brain and other physiological functional responses[19]. Various studies showed that Non-invasive brain stimulation of primary motor and premotor area modulate the neural activity and re-balance the cortico-cerebellar circuit thereby improving the motor symptoms[12]. rTMS induces the repetitive session of transcranial magnetic stimulation at the preset area of the scalp to modulate the brain excitability level. It controls or reverses the abnormal activity of brain.[6]

rTMS is equipped with both low and high frequency current, the low frequency current decreases the cortex excitability and high-frequency current thus increase cortex excitability, rTMS identified as a useful advancing method for treating neurological symptoms of individuals [23,5]. The clinical utility of non-invasive cranial Stimulation (rTMS) in Parkinson's disease needs to be explored.

AIM OF THE STUDY:

The aim of the study was to determine the therapeutic effect of Non-Invasive Brain Stimulation techniques by using rTMS (Repetitive Transcranial magnetic Stimulation) on motor functions and cognitive domains in individuals with Parkinsons disease.

METHODOLOGY:

This two-group study enrolled male and female participants between 50 and 75 years of age with a confirmed diagnosis of Parkinson's disease. Baseline evaluation of motor and cognitive function was carried out using the Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS, Part III) and the Montreal Cognitive Assessment (MoCA). Ethical clearance was obtained from the Institutional Ethics Committee of Punjabi University (Ref. No. 26/55/IEC/PUP/2022). Participants were enrolled from multiple physiotherapy and rehabilitation centers in Patiala. The study was implemented at the Patiala Neuroots Neuro-Rehabilitation Center and the Neurophysiotherapy Rehabilitation Unit within the (Department of Physiotherapy) Punjabi University, Patiala. Recruitment was facilitated through referrals from senior neurophysicians and neurosurgeons across various regions of Patiala. Each participant received an information sheet available in both Hindi and English detailing the study's aims, procedures and interventions. Written informed consent was obtained from all participants prior to their inclusion in the study.

INTERVENTIONS:

A total of ten participants were enrolled in the study, with six assigned to the experimental group and four to the control group. Eligible participants were males or females between 50 and 75 years of age, diagnosed with Parkinson's disease at stages I–III based on the modified Hoehn and Yahr scale. Only individuals presenting with mild to moderate cognitive impairment were included. Individuals were excluded if they had systemic illnesses, metallic implants larger than 10 cm^2, cardiovascular or respiratory disorders, a history of multiple head injuries, any neurological disorder other than Parkinson's disease or cerebral tumors identified on CT scans. Prior to recruitment, the investigator prepared a computer-generated randomization schedule. Participants were randomly allocated into one of two groups: the experimental group received repetitive transcranial magnetic stimulation (rTMS) or the control group received sham rTMS. After baseline assessments, participants in the experimental group (Group A) received rTMS combined with conventional physiotherapy, whereas those in the control group received sham rTMS alongside conventional physiotherapy.

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Experimental Group: rTMS (repetitive Transcranial Magnetic Stimulation) Group:
This was a non-invasive method in which participants were in a comfortable position. Then handheld, 7 cm figure-8 coil was used for treatment by which the right abductor hallucis muscle was activated by stimulating the Supplementary Motor Area (SMA) 3 cm anterior to that location and with the handle pointing to the right side and moving along the sagittal midline, find a position–1-4 cm anterior to the cranium. The stimulus intensity was set to 90% of resting motor threshold and the frequency will be set to 10 Hz+ intensity 90% of RMT+1000 pulses for 10 minutes per session -5 days for 2 weeks [25,9,12].

Control Group (sham-rTMS):
rTMS was used as a controlled condition that provided sensory perception identical to that of actual rTMS but was unable to change cortical excitability. To prevent the magnetic field from stimulating the motor cortex, the coil was positioned at a 90-degree angle [12].

Conventional Physiotherapy Training:
Participants were receive standard physical therapy intervention including breathing exercises, flexibility exercises, resistance training, pulmonary rehabilitation, gait training, treadmill training, improved gait and mobility of people with Parkinson's disease, body weight-supported treadmill training, dual task performance on a treadmill, balance training including static and dynamic balance, standing balancing on the floor with eyes open, balance on foam with first wider base of support and balance training with static and dynamic balance. Swiss balls were used for sitting balance exercises. Active range of motion drills, strengthening drills and progressive resistance training[1].

RESULTS:

Patient intervened with rTMS+ Conventional physiotherapy shows much improvement as compared to sham-rTMS.

	Day 0	Day 7	Day 15	Mean difference (0-15 days)	F value	P value	Significance level
Group A	45.00±11.61	34.33±9.42	24.17±8.19	20.83±4.36	6.451	**P<0.05**	**Significant**
Group B	36.00±15.21	29.75±10.14	26.50±9.47	9.50±5.92	0.660	p>0.05	Non-significant

Table 1: Demonstrates the Comparison of mean value and f-statistics of MDS-UPDRS at various intervals within Groups A and B. On Day 0, Day 7 and Day 15 for Group A, the mean values of the MDSUPDRS were 45.00±11.61, 34.33±9.42, and 24.17±8.19, respectively p<0.05 for Group A shows statistically significant improvement.

	Day 0 (Mean± SD)	Day 7 (Mean± SD)	Day 15 (Mean± SD)	Mean difference (0-15 days)	F value	P value	Significance level
Group A	23.33±4.27	25.33±3.33	27.00±2.00	3.67±2.73	1.820	P>0.05	Non-Significant
Group B	24.75±2.06	25.25±1.71	25.50±2.08	0.75±0.50	0.152	p>0.05	Non-significant

Table 2: Demonstrates the MOCA mean value and t-statistics at various intervals within Groups A and B. On Day 0 and Day 15 for Group A, the mean values of the MOCA were 23.33±4.27, 27.00±2.00 while for group B is 24.75±2.06, 25.50±2.08 respectively. p>0.05 shows statistically non-significant but clinically improvement was there.

DRS	Day 0	Day 7	Day 15	Mean difference (0-15 days)	F value	P value	Significance level
Group A	2.17±1.47	1.50±0.84	0.67±0.52	1.50±1.05	3.245	P>0.05	Non-Significant
Group B	2.00± 0.82	1.50±0.58	0.75±0.50	1.25±0.50	3.800	p>0.05	Non-significant

Table 3: Demonstrates the DRS mean value and f-statistics at various intervals within Groups A and B. On Day 0, Day 7, and Day 15 for Group A, the mean values of the DRS 2.17±1.47, 1.50±0.84, 0.67±0.52 while for Group B were 2.00± 0.82, 1.50±0.58, 0.75±0.50 respectively. . p>0.05 shows statistically non-significant but clinically improvement was there.

PD-QL	Day 0	Day 7	Day 15	Mean difference (0-15 days)	F value	P value	Significance level
Group A	67.00±22.83	57.00±21.83	45.00±19.32	22.00±1370	1.595	P>0.05	Non-Significant
Group B	66.50±19.91	61.25±19.62	56.00±19.30	10.50±2.89	0.287	p>0.05	Non-significant

Table 4: Demonstrates the PD-QL mean value and t-statistics at various intervals within Groups A and B.

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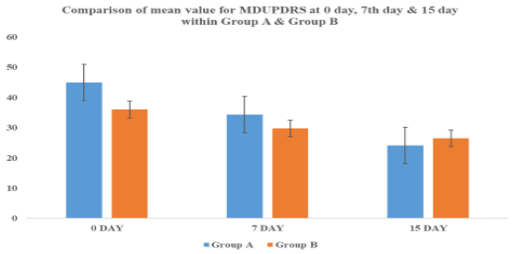
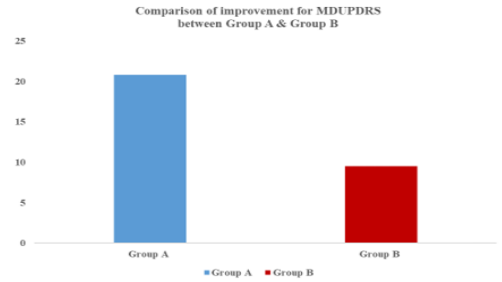
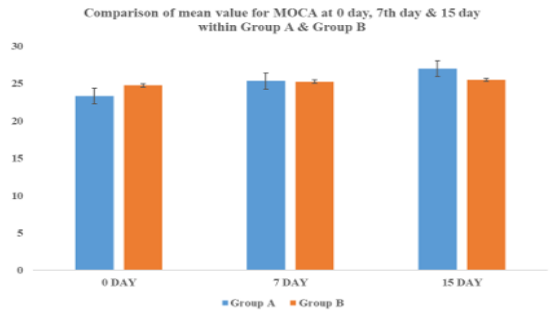
On Day 0, Day 7, and Day 15 for Group A, the mean values of the PD-QL while for Group B were respectively.p>0.05 shows statistically non-significant but clinically improvement was there.



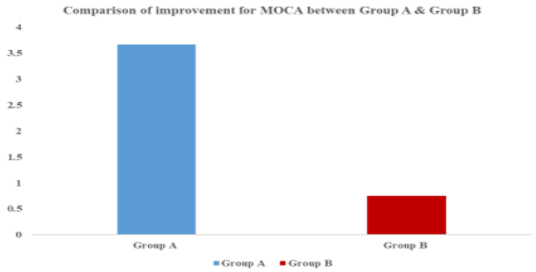
Graph 1.1: mean value for MDSUPDRSvalue for MDSUPDRS at day 0, 7th day, 15 day within group



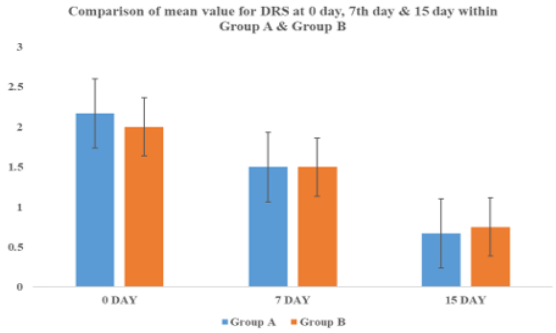
Graph 1.2: Comparison mean value for MDSUPDRS value for MDSUPDRS at day 0, 7th day, 15 day within group



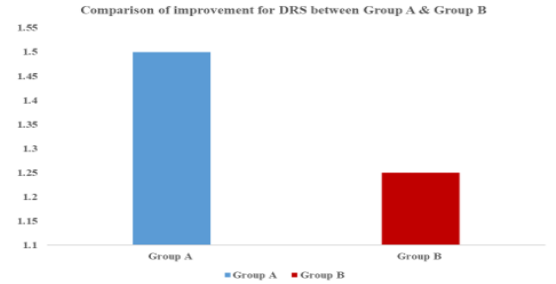
Graph 2.1: mean value for MOCA at day 0, 7th day, 15 day within group A & group B



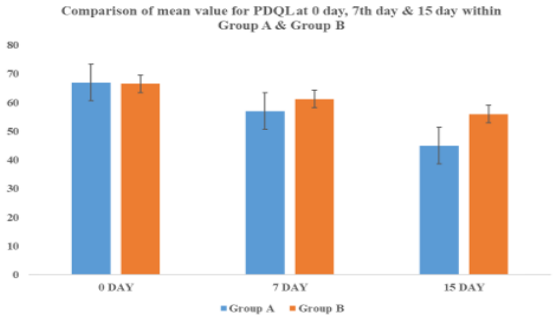
Graph 2.2: Comparison of mean value for MOCA at day 0, 7th day, 15 day within group A



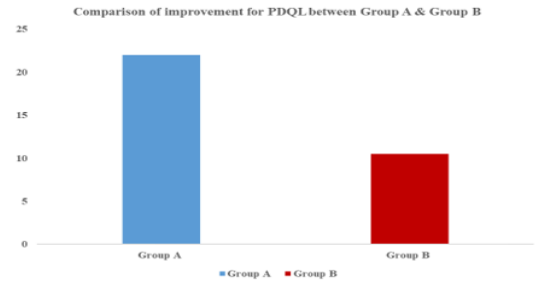
Graph 3.1: mean value for DRS at day 0, 7th day, 15 day within group A & group B



Graph 3.2: Comparison of mean value for DRS at day 0, 7th day, 15 day within group A & group B



Graph 4.1: mean value for DRS at day 0, 7th day, 15 day within group A & group B



Graph 4.2: Comparison mean value for DRS at day 0, 7th day, 15 days within group A & group B

DISCUSSION

Parkinson's disease is a Central nervous system's neurodegenerative disease that manifests both motor and non-motor symptoms worsen with increasing age. This study investigated the motor and cognitive functions of Parkinson's disease patients are improved by a Non-Invasive technique rTMS in

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which repetitive magnetic stimulations to brain is applied. Real stimulation over the M1 hand region, superficial electrical stimulation over the SMA (defined as 3 cm anterior to the motor hotspot), superficial electrical stimulation over the DLPFC (defined as 5.5 cm prior to the motor hotspot) or a sham stimulation (using a "realistic" approach) were the possibilities [25]. Numerous diagnostic scales are available to help healthcare professionals determine the degree or stages of an individual and build a treatment strategy. There are few options for improving the motor and non-motor symptoms of Parkinson's disease; the majority of treatments are conservative which have drawbacks and slow recovery especially in Deep brain stimulations there are various side effects like mood disorders, increase in number of suicidal attempts in PD patients [2]. However, there was need of advance treatment technique having effective in reducing symptoms by modulating the brain activity and offering major clinical advantages by promoting brain plasticity[4].

A number of neurological diseases, including Parkinson's disease have been treated using non-invasive brain stimulation techniques. This study provides convincing evidence for the effectiveness of rTMS in treating PD patients by treating motor and cognitive domains. Additionally, it appears that the effects of rTMS are long-lasting and unaffected by the patient's pharmaceutical status. Overall, the findings of our study demonstrated the beneficial effects of rTMS in all motor domains when employing the MD-UPDRS. However, domains of cognition exhibited effect by improving mood, executive functioning, attention and also improvement in patient's independence and quality of life by increasing functioning, and their level of disability decreases.

Repetitive transcranial magnetic stimulation (rTMS) is a form of brain stimulation. It is a non-invasive, affordable and safe method for stimulating the brain. The development of rTMS is intended to control electrical activity in the brain. The use of rTMS in various forms of neurological rehabilitation has been found to be beneficial. Although some rTMS-based research on motor function and cognition has produced some effects see Goodwill et al. (2017);Cheng et al. (2022) but there was no study which shows combined effects of rTMS on both motor and cognition as Cognitive processes such as memory, orientation, attention, executive functions determine motor performance to a large extent and adequate performance of motor tasks requires a strong interaction between planning, attention, executive functions, memory and motor learning and both are interlinked. Patients with PD have reported positive effects of rTMS, particularly when the left DLPFC is the targeted. In this handheld device is used 7 cm figure-eight coil to stimulate the SMA or DLPFC. The positioning of coil should be 1-4 cm anterior to cranium. Treatment was given with the stimulus intensity was set 90% of RMT + 1000 pulses for 10 minutes per session for 5 days 2 weeks[25, 12].

The mean value and standard deviation between the group in the comparison analysis for the MDS-UPDRS at various time points on Day 0 were 45.00±11.61 and 36.00±15.21 for Group A (Experimental Group) and Group B (Control Group) respectively, with a t-value of 1.066 and a $p<0.05$. These statistical results were significant within group but showing non-significant results between the group. Although group comparison of mean score values for Group -A revealed statistically as well as clinically significant results and faster improvement was observed in the participants. Compared to Group B, there was a noticeable improvement in balance, gait and posture but no improvement in tremors, reaction time or bradykinesia was observed whether there were improvements in all motor parameters, including gait, bradykinesia, tremors, increasing reaction timing for particular activities of the individual, postural control, balance and coordination were observed in group A. According to Chung et al. (2020), rTMS modulating brain activity and reduces uncontrollable movements such as tremors. The findings of the current study indicate that the MDS-UPDRS scores of group A significantly improved after the application of rTMS. The left SMA is stimulated with rTMS, which modulates the excitability of prefrontal cortex and helps in motor recovery. The findings of our study are consistent with [22,25] who demonstrated that rTMS applied to the SMA at an intensity of 10 Hz with RMT 90% is effective in improving motor function[11].

Whereas for Cognition the mean value and standard deviation in the comparison analysis for the MOCA at various time points on Day 0 and Day 15 were 23.33± 4.27 and 27.00± 2.00 respectively with t-value 3.287 and $p<0.05$ for Group B mean ± SD were 24.75± 2.06 and 25.50± 2.08, t-value 3.000 and a $p<0.05$ which shows statistically non-significant results but some cognitive functions, including attention, executive functioning and calculations were clinically improved in Group A. In contrast, Group B showed less improvement with their level of cognition changes from days 0 to 15. Disability also reduced when patient intervened with rTMS+ conventional physiotherapy and quality of life increases clinically but not significantly. The mean value and standard deviation in the comparison analysis for the DRS at various time points on Day 0 were 2.17± 1.47 and 2.00± 0.82 respectively, with a t-value of 3.503 and a $p< 0.05$. These results are

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statistically significant. The average MOCA score at Day 15 was 0.67± 0.52 for Group A and 0.75± 0.50 for Group B, with a t-value of 5.000 and a p <0.05. The findings of the current study which modulates the excitability of prefrontal cortex and helps in motor recovery and leads to decrease in disability. The findings of our study are consistent with [14] who demonstrated that cranial rTMS application at an intensity of 10 Hz with RMT 90% of 1000 pulses for 20 min is effective in decreasing Disability.

For Quality of life the mean values of the PD-QL were 67.00± 22.83, 45.00± 19.32 on Day 0 and Day 15 for Group A, and 66.50± 19.91, 56.00± 19.30 on Day 0 and Day 15 for Group B, respectively. The mean PD-QL values in both groups declined, which indicates that the level of disability as measured on the scale from day 0 to day 15 decreased as well. Both group A (22.00± 13.70) and group B (10.50± 2.89) had a decline in values, according to the mean difference between the pre- and post-values of the two groups. The calculated t-values for groups A and B were respectively 3.934 and 7.275. According to the current investigation, all MDS-UPDRS measures for Group A statistically and clinically significantly ($p<0.05$) improved when provided via the MDS-UPDRS. All aspects of Group A, where rTMS was used to intervene, were improved. In Group B, improvements were also observed but some aspects remained unrecognized. The MOCA scale has been used to assess cognition, but its findings have not been conclusively demonstrated. Nevertheless, in Group A, the participants' executive functioning, attention, calculation and mood improved, and their MOCA clinical scores increased, whereas in Group B, the scores remained essentially unchanged and no such improvement was noted.

The DRS was used to quantify disability and both statistically and clinically, there was a decline in participants' levels of disability in both groups. Both statistically and clinically, the quality of life of Group A improved in quality of life of Group B also improved, albeit with a minimal decrease in the mean value. According to the results of the current study, conventional physical therapy combined with non-invasive cranial stimulation (rTMS) is an efficient and safe treatment for Parkinson's disease when administered over the course of 15 days. Due to small sample size the results of the current study was Non-significant statistically. The limited sample size used in this study makes it challenging to draw conclusive findings.

CONCLUSION:

Non-invasive Cranial stimulation is an emerging neuromodulation method for treating various neurological conditions, such as Parkinson's disease. Among these methods, repetitive transcranial magnetic stimulation is most commonly used in the fields of basic neuroscience and clinical applications. However, the present work is discrete in its implementation of rTMS along with conventional rehabilitation for a period of two weeks in which multitarget transcranial direct current stimulation of the primary motor cortex and left dorsolateral prefrontal cortex induced immediately after effects on the scores of the MDS-UPDRS for motor, MOCA for cognition, DRS for disability, PD-QL for quality of life and mainly reduced freezing episodes of gait and improvements in executive function and mobility. The rTMS emphasized in the present study is an insight for enhancing motor recovery and improving cognitive functioning by stimulating the targeted area to determine their effect on overall improvement in individuals with Parkinson's disease.

LIMITATIONS OF THE STUDY:

There are a few shortcomings in the current study that must be considered. The limited sample size used in this study makes it challenging to draw conclusive findings. Additionally, the study considered the unequal distribution of participants, both in the experimental and control groups. Additionally, the long-term effects of rTMS could not be studied because of the short duration of treatment. The long-term effects of rTMS could not be examined further because of the short treatment period. A gender-based comparison was also impossible because of the considerably smaller proportion of female participants, in addition to these limitations. Thus, the study was entirely based on clinical outcomes. Although these limitations give an opportunity for improvement and for more researches.

FUTURE SCOPE OF THE STUDY:

1. There is a need of larger sample size to generate Statistically significant results
2. Due to limited number of studies on PD, other controlled conditions including age, Gender and other parameters need to be considered in future studies.
3. The effect of various parameters of rTMS needs to be taken into consideration for future research.
4. Future research may focus on long duration intervention and post-intervention monitoring.

CONFLICT OF INTREST:

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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