The Egyptian Journal of Hospital Medicine (October 2020) Vol. 81 (6), Page 2160-2164

The role of Therapeutic Repetitive Transcranial Magnetic Stimulation in Treatment of Sleep Disorders in Parkinson's disease Patients

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Abstract
Background: Parkinson's disease (PD) is the most common movement disorder and represents the second most common degenerative disease of the central nervous system.
Objective: To measure the effect of repetitive transcranial magnetic stimulation (rTMS) as therapeutic treatment on sleep disorders in patients with Parkinson's disease (PD).
Patients and methods: This double-blinded study included 20 PD patients (10 received real rTMs and 10 received sham rTMs) patients recruited from Inpatient and Outpatient Clinic of Neuropsychiatric Department of Aswan University Hospital. Our patients were divided into 2 groups (10 patients each). **Results:** As regards the effect of rTMs on PDSS and sleep latency, our study results found no significant change in Parkinson disease sleep scale between both groups but there was significant change in sleep latency that it decreased in the group received real rTMS in comparison with the SHAM group. In addition, there were significant changes in wake stage and rapid eye movement stage that both decreased in response to rTMS while there was no significant changes in non-rapid eye movement stage. Awakening after being asleep on both studied groups showing significant decrease in wake after sleep onset and wake after persistent sleep as both of them decrease wit rTMS. **Conclusion:** The main finding of this study was that 10 sessions of 20–Hz rTMS applied over both parietal area improved the subjective as well as the objective sleep quality as reflected by a decrease of frequency in arousal from sleep and in Non-REM–1 stage sleep.
Keywords: Parkinson's disease, Transcranial Magnetic Stimulation, Sleep Disorders.

INTRODUCTION

Complaints of disordered sleep are reported in 60 to 98% of Parkinson's disease (PD) patients, being one of the most frequent non-motor symptoms and contributing significantly to the decreased quality of life in PD. PD patients suffer mostly from impaired sleep maintenance and increased sleep fragmentation **(1).**

The pathophysiology of sleep disorders in PD patients has not been fully elucidated. A primary factor is degeneration of central sleep regulation centres in the brainstem **(2).** Sleep disorders in PD may also be secondary to dopaminergic medication, nocturnal akinesia and non-motor symptoms such as depression and restless legs syndrome **(3).** Recent evidence suggests that also dopaminergic dysfunction in the hypothalamus, whether disease or medication-related, contributes to sleep disorders in PD **(4)**.

The effect on sleep was investigated with a self-assessment scale by **Khedr *et al.*** **(5)** who found improvement after the stimulation applied over primary motor cortex (PMC). Another study reported objective improvement of patients' sleep profile after the stimulation over parietal cortex but not over PMC **(6).** However in that study sleep was recorded with actigraphy, a diagnostic tool considered to be less sensitive than nocturnal polysomnography (PSG), especially in determining the percentage of particular sleep stages, occurrence of EEG arousals and the presence of sleep-related breathing disorders. The improvement of sleep quality after the stimulation over parietal cortex was explained by documented involvement of this area in sleep regulating processes. The stimulation of PMC may improve sleep as an outcome of the alleviation of motor symptoms **(7).**

Transcranial magnetic stimulation (TMS), a tool for noninvasive magnetic stimulation of the cerebral cortex **(4),** is used as an experimental non pharmacological therapy in PD with variable effects on motor symptoms in PD patients **(8)**. In healthy participants, rTMS can affect sleep structure both when applied during sleep and prior to sleep **(9).** In spite of the high prevalence of sleep disorders in PD patients, the effect of rTMS on sleep in PD patients has not previously been studied objectively.

In the recent years, there is an increasing interest in application of rTMS in the treatment of patients with insomnia, and it seems that rTMS might have the potential to improve sleep **(10)**, but negative results were also reported **(11).**

The aim of the work was to measure the effect of rTMS as therapeutic treatment on sleep disorders in patients with PD.

PATIENTS AND METHODS

This double-blinded study included 20 PD patients started and the 20 PD (10 real, 10 sham) patients that were recruited from Inpatient and Outpatient Clinic of Neuropsychiatric Department of Aswan University Hospital completed the study.

Received:22 /7 /2020
Accepted:21 /9 /2020

Inclusion criteria:

Patients with Parkinson disease as diagnosed by brain bank criteria for diagnosis of PD that have history of sleep disturbance fulfilled by Parkinson disease sleep scale.

Exclusion criteria:

1-Patients with PD with disturbed conscious Leve.

2-Sever cognitive impairment.

3- Psychosis and medical problems as renal failure, liver cell failure, respiratory failure and endocrinal impairment.

4-Patients with other types of Parkinsonism as Multisystem atrophy supranuclear palsy and encephalitic Parkinsonism.

5- Patients had contraindication of magnetic stimulation (metallic piece, pace maker and epilepsy).

Patients were asked to complete all sessions and could not change their regime of medication throughout the study.

Our patients were divided into 2 groups (10 patients each): 1st group: received real rTMS which was done by using high frequency rTMS (20 hz) 70% of the resting motor threshold, 10 train each train 20 second with 10 second interval with total 2000 pulse for each hemisphere (parietal area) 5 sessions\week daily for 2 successive weeks. **2nd group:** received sham rTMS that was done at the same area of the real rTMS 5 sessions\week daily for 2 successive weeks.

Ethical approval and written informed consent:

An approval of the study was obtained from Aswan University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

All patients were subjected to the following:

1. Complete Medical and neurological assessment for diagnosis of PD by using Brain Bank Criteria for diagnosis of Parkinson disease, assessment of the severity of PD by using Parkinson disease rating scale, history suggestive of sleep disorders assessed by using Parkinson disease sleep scale and assessment of cognitive function by using Minimental state examination (MMSE).
2. Polysomnography: That was done two times, first at the start of study to diagnose type of sleep disorders, second after receiving rTMS. This polysomnography systematically monitored the electroencephalogram (EEG) (C3-A2,C4-A1), electrooculogram (EOG), electromyogram of the chin (EMG), electrocardiogram (ECG), body positions, nasal and oral airflow, thoracic and abdominal effort, limb movements, pulse oximetry, and snoring sound level. It was done at Chest Department of Aswan University (because of the availability of the set).
3. rTMS procedure: At first we assessed the resting motor threshold to determine 70% for each patient. Our patients were divided into 2 groups (10 patients each). **1st group** received real rTMS, which was done by using high frequency rTMS (20 hz) 70% of the resting motor threshold, 10 train each train 20 second with 10 second interval with total 2000 pulse for each hemisphere (parietal area). Each patient received five sessions /week daily for two consecutive weeks with 10 total sessions. The parietal area was determined according to 10-20 system for electroencephalographic electrode positioning at P3 and P4 respectively. **2nd group** received sham rTMS that was done at the same area of the real rTMS.
4. The two groups of patients underwent Polysomnography for the second time to compare the therapeutic and sham rTMS effect on the sleep disorders.
5. Follow up was done after ten sessions of rTMS, for assessment of sleep disorders using Polysomnography and Parkinson disease sleep scale.

Statistical analysis

To check homogeneity between groups before the start the stimulation protocol (at PRE), a Students ‘‘t’’ test for independent samples, was applied for each variable. Afterwards, to evaluate the effect of the stimulation, a two-way ANOVA with repeated measures was performed for each of the variables analysed. One within-subjects factor was defined, factor evaluation with 3 levels (PRE, POST, POST-2); this would therefore measure the effect of the protocol on the variables. The between subjects factor was the group (real stimulation or sham stimulation), which therefore was set to measure a possible placebo effect. During analysis the normality of distribution was checked by a K–S test. In the ANOVA analysis of the degrees of freedom were corrected by applying the Greenhouse–Geisser correction when sphericity was violated. The SPSS version????? package was used for statistical analysis. Significance was set at $p \leq 0.05$.

RESULTS

Table (1) showed difference between both studied groups pre-intervention in age, Unified Parkinson Disease rating scale, minimental scale examination, resting motor threshold and Parkinson disease sleep scale revealing that there was no significant difference between both groups.

Table (2) showed difference between both studied in Percentage of each sleep stage (Wake, Non Rapid Eye movement and Rapid Eye movement) revealing that there was no significant difference between both groups.

Table (3) showed difference between both studied groups in number of apneas, number of hypopneas and apnea hypopnea index that indicated no significant difference between the 2 groups.

Table (4) showed difference between both studied groups in number of awakenings, wake after sleep onset and wake after persistent sleep showing no significant difference between both groups.

Table (5) showed difference between both studied groups in desaturation information including

desaturation index at threshold 3% in supine position, average oxygen saturation and the lowest oxygen saturation showing no significant difference between both groups.

Table (6) showed difference between both studied groups in electrocardiography rates while the patient is awake and during sleep including maximum, minimum and average heart rates showing no significant difference between both groups.

Table (7) showed effect of rTMS on Parkinson disease sleep scale and sleep latency on both studied groups showing no significant change in Parkinson disease sleep scale between both groups but there was significant change in sleep latency that it decreased in the group received real rTMS in comparison with the sham group.

Table (1): Baseline characteristics for the patients in both groups

Variable	Baseline data of studied groups		
	real rTMS Mean ± SD	**sham rTMS Mean ± SD**	**P value**
Age	63.70 ± 9.49	61.20 ± 14.94	0.684
UPDRS Mental	6.00 ± 1.83	5.80 ± 2.25	0.796
UPDRS Motor	76.30 ± 9.75	70.30 ± 17.69	0.631
Total MMSE	27.89 ± 1.27	27.90 ± 1.20	0.999
RMT %	0.34 ± 0.06	0.38 ± 0.05	0.280
PDSS	44.70 ± 2.98	43.20 ± 4.83	0.683

*Mann-Whitney test

UPDRS; Unified Parkinson Disease Sleep Scale, MMSE; Mini mental State Examination, RMT; Resting Motor Threshold, PDSS; Parkinson's Disease sleep scale, N1; Stage 1 sleep, rTMS; repetitive transcranial magnetic stimulation.

Table (2): Percentage of sleep stages pre intervention in both groups

Variable	Percent of Stages		
	real rTMS Mean ± SD	**sham rTMS Mean ± SD**	**P value**
Wake	16.0 ± 10.0	10.2±4.2	0.143
NREM			
N1 (stage 1)	24.9 ± 11.6	28.8 ± 20.5	0.912
N2 (stage 2)	36.1 ± 14.3	32.3 ± 13.3	0.436
N3(stage 3)	19 ± 12.7	24.1 ± 13.0	0.218
REM1	19.9 ± 7.0	14.7 ± 4.7	0.143

*Mann-Whitney test

REM; Rapid eye movement ,N1;stage 1 sleep,N2;stage 2 sleep,N3;stage 3 sleep, NREM; Non-rapid eye movement, rTMS; repetitive transcranial magnetic stimulation.

Table (3): Number of apneas, and hypopneas and apnea hypopnea index pre intervention in both groups

Variable	Apnea summary		
	real rTMS Mean ± SD	**sham rTMS Mean ± SD**	**P value**
total Apnea	11.3 ± 7.4	11.0 ± 7.0	0.631
REM Apnea	2.8 ± 2.6	1.6 ± 1.8	0.315
NREM Apnea	8.5 ± 5.8	9.4 ± 7.2	0.853
total hypopnea	49 ± 29	36 ± 23	0.0579
REM hypopnea	14 ± 10	4 ± 4	0.035
NREM hypopnea	35 ± 24	32 ± 23	0.739
AHI1: Apnea Hypopnea Index	20.0 ± 12.4	15.0 ± 9.3	0.432
REM AHI	20.9 ± 15.5	11.7 ± 10.9	0.28
NREM AHI	19.9 ± 12.8	15.7 ± 10.3	0.481

*Mann-Whitney test

AHI; Apnea hypopnea index, REM; Rapid eye movement, NREM; Non-rapid eye movement, rTMS; repetitive transcranial magnetic stimulation.

Apnea hypopnea index (AHI) is an index used to indicate the severity of sleep apnea. It is represented by the number of apnea and hypopnea events per hour of sleep.

Table (4): Awakening arousal association pre intervention in both groups

Variable	Awakening arousal association		
	real rTMS Mean ± SD	sham rTMS Mean ± SD	P value
Number of awakenings	3.00 ± 1.63	3.20 ± 1.69	0.769
Wake after sleep onset (duration in minute)	39.25 ± 28.60	23.05 ± 9.41	0.315
Wake after persistent sleep (duration in minute)	38.55 ± 28.87	23.05 ± 9.41	0.315

*Mann-Whitney test rTMS; repetitive transcranial magnetic stimulation.

Table (5): Desaturation information pre intervention in both groups

Variable	Desaturation information		
	real rTMS Mean ± SD	sham rTMS Mean ± SD	P value
desaturation index 1 threshold 3% in supine position	14 ± 7.2	11.3 ± 11.4	0.315
Average SaO2	0.9 ± 0.	0.9 ± 0.1	0.218
the lowest So2 %	0.7 ± 0.1	0.7 ± 0.1	0.631

*Mann-Whitney test SO2; oxygen saturation, rTMS; repetitive transcranial magnetic stimulation.

Table (6): Electrocardiography **(**ECG) rates pre intervention in both groups

Electrocardiography Rates	EKGRates1		
	real rTMS Mean ± SD	sham rTMS Mean ± SD	P value
Maximum awake	144 ± 54	134 ± 51	0.631
Minimum awake	72 ± 38	60 ± 28	0.436
Average awake	99 ± 38	88 ± 24	0.579
Maximum asleep	176 ± 58	138 ± 51	0.123
Minimum asleep	48 ± 18	49 ± 23	0.971
Average asleep	90 ± 20	85 ± 18	0.546

*Mann-Whitney test. rTMS ;repetitive transcranial magnetic stimulation.

Table (7): Effect of rRTMs on PDSS and Sleep latency.

real rTMS			sham rTMS		P value		
	Pre session Mean ± SD	Post session Mean ± SD	Pre session Mean ± SD	Post session Mean ± SD	(pre-post) real rTMS (changes)	(pre-post) SHAM rTMS Changes	(Pre- post session real versus sham)
PDSS	44.7 ± 2.98	37.2 ± 5	43.2 ± 4.8	38.1 ± 5.7	-7.50 ± 4.60	-5.10 ±	.1900
N1Latency (sleep latency) (minute)	55.8 ± 29.5	32.7 ± 28.9	34.3 ± 16	42.1 ± 19.8	-23.1 ± 32.4	3.98 7.9 ± 29.2	**. 049*0**

PDSS; Parkinson disease sleep scale, rTMS; transcranial magnetic stimulation.

DISCUSSION

This double-blinded study was conducted on 20 patients with PD who had sleep disorders, who were recruited from Inpatient and Outpatient Clinic of Neuropsychiatric Department of Aswan University Hospital. Our patients were divided into 2 groups (10 patients each). 1st group who had real rTMS which was done by using high frequency rTMS (20 hz) 70% of the resting motor threshold, 10 train each train 20 second with 10 second interval with total 2000 pulse for each hemisphere (parietal area). Second group who had sham rTMS that was done at the same area of the real rTMS. In our study, there were statistical insignificant differences between both studied groups pre-intervention in age, Unified Parkinson disease rating scale, mini-mental scale examination, resting motor threshold and Parkinson disease sleep scale, which indicate good randomization between both groups. Also, there were statistical insignificant differences between both studied groups pre-intervention in percentage of each sleep stage (Wake, Non Rapid Eye movement and Rapid Eye movement), apnea summary, awakening arousal association, arousal association, periodic leg movements, leg movements, desaturation information, and (ECG) heart rates as $p > 0.05$.

As regards the effect of rTMs on PDSS and Sleep latency, our study results found no significant change in Parkinson disease sleep scale between both groups but there was significant change in sleep latency that it decreased in the group received real rTMS in comparison with the sham group. In addition, there

were significant changes in wake stage and rapid eye movement stage that both decreased in response to rTMS while there was no significant changes in non-rapid eye movement stage. Awakening after being asleep on both studied groups showed significant decrease in wake after sleep onset and wake after persistent sleep as both of them decreased wit rTMS .

This is in agreement with **Antczak *et al.*** [12] study that was conducted on 11 PD patients who underwent ten daily rTMS sessions at 15 Hz and found that the rTMS reduced episodes of light sleep (N1%) (20.0 ± 8.4 vs 12.0 ± 5.7 % $p < 0.01$) and the arousal index (AI) (12.2 ± 9.0 vs 8.7 ± 6.3 $p < 0.04$). The rTMS also improved the subjective sleep assessment as reflected by the increase in PDSS score (95.8 ± 23.4 vs 106.4 ± 24.6 with $p < 0.02$). Our study has been conducted at 20 Hz. Our study found significant change in periodic leg movement index with no significant change in leg movement associated with micro-arousal, with awakening and with respiratory event. This disagrees with **Antczak *et al.*** [12] who reported there was lack of change in periodic limb movements (PLM) and sleep-related breathing disorders.

The decrease in stage 1 (N1%) in our patients is a consequence of the lower arousal index AI. According to the standard rules of sleep-scoring [13], the presence of arousal indicates a change from N2 to N1. The number of REM hypopnea also decreased in response to rTMS. Apnea Hypopnea Index decreased in response to rTMS. NREM apnea hypopnea index decreased with rTMS, while there was no significant change in hypopnea. This is supported by earlier data of **Askenasy *et al.*** [12] who described greater prevalence of arousals during light sleep in PD patients. The lack of change in periodic limb movements (PLM) and sleep-related breathing disorders supports the opinion that the AI improvement was related to the improvement in motor symptoms of PD, rather than in the improvement to these sleep specific disorders. Another possible explanation for the polysomnographic improvement may be the modulation of cortical excitability by rTMS, which has a direct influence on the physiologic mechanisms of sleep. **Graf *et al.*** [9] study observed a reduction in the percentage of N1 sleep. However, the site of the stimulation was located over the left dorsolateral prefrontal cortex. While **De Gennaro *et al.*** [14] rTMS in the paired associative protocol was applied to PMC, an enhancement of the slow wave activity occurred without producing any change in the parameters of sleep macrostructure that were examined in our study**.** A standard 5 Hz rTMS applied over PMC in a protocol similar to the paired-associative method induced an increase in the slow wave activity. A standard 5 Hz rTMS applied over PMC in a protocol similar to the paired-associative method induced an increase in the slow wave activity.

Van Dijk *et al.* [6] study reported the effect of rTMS on sleep parameters, which included an improvement in two out of seven actigraphic variables, fragmentation index, and sleep efficiency in a group of patients receiving focal parietal stimulation.

CONCLUSIONS

The main finding of this study is that 10 sessions of 20–Hz rTMS applied over both parietal area improved the subjective as well as the objective sleep quality as reflected by a decrease of frequency in arousal from sleep and in non-REM–1 stage sleep. This improvement was probably associated with alleviation of the nocturnal symptoms by rTMS rather than any modulation of the mood or the motor cortex excitability. Further longitudinal studies are needed to assess rTMS effect on sleep quality in patients with PD including larger sample size.

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