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Effect of Repetitive Transcranial Magnetic Stimulation on Essential Tremors

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ABSTRACT

Background: The effects of cerebellar low-frequency repetitive transcranial magnetic stimulation (rTMS) in individuals suffering from essential tremor (ET) are controversial.

Aim of The Work: To evaluate repetitive transcranial magnetic stimulation (rTMS) can help people with essential tremors.

Patients and Methods: This case study involved 30 subjects divided into an active group of 15 ET patients and a sham group of another 15 ET patients who were treated in tertiary care at Al-Hussein and Sayed Galal Hospitals, Al-Azhar University. The Fahn, Tolosa, Marin (FTM) Tremor Rating Scale has been used to evaluate and scale tremors at baseline, as well as a day, one month, two months, and three months following the (sham and active) repetitive transcranial magnetic stimulation sessions.

Results: The results of this study showed that repeated active rTMS over the cerebellum enhanced total and specific subcores (tremor, drawing, and functional disability).The influence lasted for 3 months following the final session. The sham group's total and specific FTM subcores (tremor, drawing, functional disability) showed no significant differences.

Conclusion: For patients suffering from severe essential tremor, cerebellar rTMS can be an effective therapy choice.

Keywords: *Repetitive transcranial magnetic stimulation; Essential tremor; Cerebellum.*

INTRODUCTION

Essential tremor (ET) is the most prevalent movement disorder, with a global prevalence rate of 3.2 instances per 1,000 people, increasing to 28.7 instances per 1,000 people in those over the age of 80. An ET is defined by an isolated upper extremity action tremor that has lasted at least 3 years and is not accompanied by any neurological symptoms. However, some individuals can experience a variety of other signs and symptoms.[1] Tremor usually worsens with age leading to increased disability of patients as well as loss of their independence.[2&3]

Several treatments are available for ET such as propranolol, primidone, topiramate, alprazolam and botulinum toxin type A injection.[4] Despite detrimental effects on life quality for patients, medications traditionally used as the first-line treatment for ET are neither effective enough nor completely safe for a considerable number of patients.[5]

Deep brain stimulation and other surgical procedures such as thalamotomy may provide better unilateral tremor control but, they are invasive and costly, and many patients prefer not to select surgical therapeutic options.[6&7] ET researchers have looked into non-invasive brain stimulation (NIBS) methods like rTMS as options to conventional ET therapies during the past decade.[8&9]

Repetitive TMS protocols are often utilized as stimulation to inhibit cortical activity in specific locations like the cerebellum to reduce tremors in ET patients.[10] The oscillating network hypothesis is the theory that these stimulation protocols are based on. They work by dynamically acting as oscillators in numerous hyperactive brain areas that could lead to tremors. [11&12] One of the possible tremor networks is the cerebello-thalamo-cortical circuit. As a result, researchers predict that by using rTMS on the cerebellum, they can diminish tremors in ET cases by tuning down hyperactive cerebello-thalamo-cortical circuits.[13] The purpose of this research was to see if rTMS can treat essential tremors and how it could change the course of tremors. In addition, it aimed to illustrate the best protocol that can be used for essential tremors.

PATIENTS AND METHODS

This study has been conducted in tertiary care units at Al-Hussein and Sayed Galal Hospitals, Al-Azhar University, on a total of 30 ET patients, divided into15 ET patients as an active group and 15 ET patients as a sham group.

Eligibility criteria

Patients over the age of 18 who have been diagnosed with ET or ET plus based on the consensus criteria for movement disorders.[14] Despite receiving suitable medical therapy, the patient must have significant residual tremors. We excluded patients with history of seizures and those on tremor-inducing medications such as central cholinergic drugs, central monoaminergic drugs, peripheral adrenergic drugs, thyroid hormone supplements, adrenocorticosteroids, anticonvulsants, bronchodilators, as well as antidepressants. We also excluded individuals who had metal or electronic devices implanted in their bodies, like aneurysm clips or coils, stents in the brain or neck, spinal cord stimulators, deep brain stimulators, metallic implants in ears and eyes, and baclofen pumps.

Methods and data collection

The selected participants have been randomized into 2 equal groups: one study (active) group and another control (sham) group with the same inclusion and exclusion criteria, and all of the patients continued on the same medical treatment they were already receiving. An active group composed of fifteen patients with Essential tremors was studied (5 males and 10 females) with a range of age between 18-70 years old. Patients in this group received 12 sessions of sham rTMS (3 sessions per week for 4 weeks). A sham group composed of fifteen patients with Essential tremors was studied (7 males and 8 females) with a range of age between 18-81 years old. Patients in this group received 12 sessions of sham rTMS (3 sessions per week for 4 weeks).

Careful history taking

Personal history: name, age, sex, residence, occupation, and particular habits of medical significance; complaint: onset, course, and disease duration; history of the present illness including history of the tremors: onset, course, duration, affected body parts, received treatment and the response, and associated symptoms; past medical history; drug and alcohol intake history; and family history.

Investigations and assessment

Other causes of tremors were excluded by careful history-taking and a full general and neurological examination. Brain MRI to exclude structural brain lesions and thyroid function tests. Clinical evaluation and scaling of tremors using the Fahn, Tolosa, Marin (FTM) Tremor Rating Scale[15] has been done for both active and sham groups at baseline,then 1 day, 1 month, 2 months, and 3 months for both active and sham groups after the rTMS sessions.

Repetitive TMS procedure

We measured the RMT of the right abductor pollicis brevis. RMT was defined as the lowest stimulus intensity necessary to induce motor-evoked potentials (MEPs) of at least 50 μV in at least five of the ten consecutive trials. The stimulation intensity in rTMS has been set to 90% of the RMT. For cerebellar stimulation, the site was set as the midpoint between the mastoid and inion. In turn, every side of the cerebellum was applied. At twelve sessions (three sessions per week, day after day for four weeks), 1800 stimulations per day were applied with a frequency of one Hz (900 stimulations to the cerebellum on every side). Each 1Hz rTMS session is comprised of 30 trains of 30 seconds each, separated by 10 seconds. Having the sham group, similar rTMS measures were considered, despite putting the coil perpendicular to the scalp.

Ethical approval

The research was accepted by our faculty's ethical committee, and patients and controls gave their informed written consent before the enrollment.

Statistical analysis of the data

Data represented as (Mean ± SE) unless otherwise indicated. The Kolmogorov-Smirnov test has been performed to test the data's normality. The Chi-square test for qualitative information or percentages and the Mann-Whitney test for non-parametric information have been employed to compare the clinical and physiological parameters of patients with active and sham stimulation.Two ways and a one-way repeated measure ANOVA was utilized to compare (FTM) scores between active and sham stimulation groups at the different times (baseline, day one after sessions 1,2, and 3 months after).If there was a significant difference between the means, the different time points have been compared using multiple comparisons with Bonferroni correction. Two sample t-test among active and sham stimulation groups; and a paired t-test among baseline and day 1 within each group. Age and duration of tremor were correlated with the TRS-A, B, C, and overall scores using the Spearman non-parametric test.For all statistical tests, a p-value of more than 0.05 is deemed not significant. A p-value of less than 0.05 is regarded as significant. A p-value of less than 0.001 is regarded as highly significant.

RESULTS

There were about 12 (40%) men and 18 (60%) women among the 30 patients studied, with an average age of 35 years in the active group and 41 years in the sham group (Table 1). There was no significant difference between sham group and active group as regard the gender, age, and tremor duration (Table 1).

There was a highly significant reduction in subscore A, B, and total score of the active group at day one, one month, two months, and three months after the sessions compared to the baseline score (Table 2). There has been a highly significant decrease in subscore C of the active group at day 1and 1 month, but not 2 months or 3 months after the sessions compared to the baseline score (Table 2).

There was no significant difference in FTM subscore A, B, C, or total score of the sham group at day one, one month, two months, or three months after the sessions compared to the baseline score (Table 3)

There was a highly significant difference in the global assessment score by the patient after treatment between the active and sham groups (Table 4). There was no significant correlation between TRS-A, B, and C and total score and patient age at baseline, day one, one month, two months, or three months after the sessions. There was also no significant correlation between TRS-A, B, and C and total score and duration of tremors at baseline, day one, one month, two months, or three months after the sessions (Table 6).

Parameters		Active stimulation (N=15)		Sham-stimulation (N=15)		Statistics test	P-Value
Gender	Male	5	(33.3%)	7	(46.7%)	Chi square test $X^2 = 0.24$	0.456 n.s.
	Female	10	(66.7%)	8	(53.3%)		
Age (years)	(Mean+SE)	35.73 ± 4.76		41.8 ± 4.75		MW test w-value =205	0.262 n.s.
	Range	(18 – 70)		Range (18 – 81)			
Tremor duration (Year)		5.5±1.56		3.13±0.42		MW test w-value =240.5	0.752 n.s.

Table (1): Participant's characteristics in active and sham-stimulation as regards demographic data.

	Active stimulation					Repeated ANOVA	
	Baseline	**Day 1**	**After 1 month**	**After 2 months**	**After 3 months**	**F-Value**	**P-value**
Subclass A	14.7±1.5 [a]	7.13±0.8 [b]	7.82±0.73 [b]	8.7±0.8 [b]	10.1±0.9 [b]	9.81	**<0.001**
T-value P-value		(T= 5.57) **(p < 0.001)**	(T= 5.08) **(p = 0.001)**	(T= 4.39) **(p < 0.006)**	(T= 3.42) (p = 0.011)		
Subclass B	14.7±1.4 [a]	7.1±0.8 [b]	7.7±0.8 [b]	9.1±0.9 [b]	9.6±0.9 [b]	9.27	**<0.001**
T-value P-value		(T = 5.44) **(p <0.001)**	(T = 5.02) **(p <0.001)**	(T = 4.02) **(p = 0.001)**	(T = 3.64) **(p = 0.005)**		
Subclass C	11.0±1.1 [a]	5.5±0.6 [c]	6.7±0.7 [b, c]	7.9±0.8 [a,b,c]	9.2±0.8 [a,b]	6.81	**<0.001**
T-value P-value		(T =4.74) **(p <0.001)**	(T = 3.70) **(p = 0.004)**	(T = 2.66) (p = 0.097)	(T = 1.56) (p = 1.0)		
Total score	40.5±3.4 [a]	19.6±1.9 [b]	22.2±1.9 [b]	25.7±2.2 [b]	28.9±2.5 [b]	10.99	**<0.001**
T-value P-value		(T = 6.03) **(p < 0.001)**	(T = 5.28) **(p < 0.001)**	(T = 4.26) **(p = 0.001)**	(T = 3.35) **(p =0.013)**		
Total score (%)	28.1%	13.6%	15.4%	17.9%	20.0%		

Means that do not share a letter are significantly different (Bonferroni pairwise comparisons method, P < 0.5)

Table (2): ANOVA of the (FTM) score of an essential tremor patient prior to and following active stimulation.

	Sham stimulation					Repeated ANOVA	
	Baseline	**Day 1**	**After 1 month**	**After 2 months**	**After 3 months**	**F-Value**	**P-value**
Subclass A	13.2 ± 1.2	12.4 ± 1.2	12.8 ± 1.15	13.1 ± 1.2	13.3 ± 1.1	0.1	0.983 n.s.
Subclass B	13.4 ± 0.9	12.6 ± 1.0	13.1 ± 1.0	12.9 ± 1.0	13.3 ± 1.0	0.11	0.980 n.s.
Subclass C	10.2 ± 0.6	9.1 ± 0.6	9.7 ± 0.6	9.9 ± 0.8	10.4 ± 0.6	0.64	0.639 n.s
Total score	36.8 ± 2.5	34.1 ± 2.6	35.7 ± 2.5	36.0 ± 2.7	37.0 ± 2.5	0.2	0.938 n.s
Total score (%)	25.6%	23.7%	24.8%	25.0%	25.7%		

Multiple comparisons using Bonferroni correction revealed that the FTM TRS-A, B, and overall scores were significantly lower in the active stimulation group at one day, one month, two months, and three months compared to baseline.

However, in the sham group, there have been no significant differencesin FTM TRS-A, B, C, and total between baseline, and immediately after 1 day, 1month, 2 and 3 months of sham stimulation.

Table (3): ANOVA of the (FTM) score of an essential tremor patient prior to and following sham stimulation.

Parameters		Active stimulation (N=15)		Sham-stimulation (N=15)		Statistics test	P-Value
Global assessment by the patient after ttt	Mean ± SE	15	2.267 ±0.118	15	-0.20 ± 0.145	MW test w-value =345	<0.001
	Median		2		0		

This table shows that there was a highly significant difference in global assessments by the patient after treatment among the active and sham groups

Table (4): Comparison between Global assessments by the patient after treatment in active and sham groups.

DISCUSSION

The age, gender, or duration of tremor of patients in the active and sham groups did not differ significantly in this study. Thus, any effect of age, gender, or tremor duration on the change in ET severity will be negligible. The effect of a course of 12 low-frequency (1 Hz) cerebellar rTMS on the severity of tremor in individuals with essential tremor was assessed in this single-blinded sham-controlled study.The Fahn-Tolosa-Marin (FTM) scale has been used to assess the severity of tremors at baseline, as well as on day one, one month, two months, and three months after intervention. The FTM scale is divided into three subscales: tremor severity rating (subscale A), motor task performance (subscale B), and functional disability (subscale C).[15]

Overall, there had been a significant influence of rTMS observed in the present study on all aspects of tremor at various points, as follows: there had been a highly significant decrease in subscale A of the active group at day 1, 1 month, and 2 months after the sessions. Furthermore, there was a significant reduction in subscale A 3 months after the sessions compared to the baseline score. There has been a highly significant decrease in the FTM total score and subscale B of the active group on day one, one month, two months, and three months after the sessions compared to the baseline score. There has been a highly significant reduction in subscale C of the active group on day 1 and 1 month, but not 2 months, or 3 months after the sessions compared to the baseline score.

These findings support and extend the findings of Gironell et al. in 2002, who reported a transient clinical decline in tremor after a single session of cerebellar stimulation.[16] and Popa et al. in 2013 who noted a significant long-term (3 week) reductionin all aspects of tremor after the application of 5 consecutive days of sessions on the posterior cerebellum bilaterally.[17] The longer advantageous impact reported in our study (3 months) is most likely due to the stimulation sessions being repeated. Also, the number of pulses in each session in our study was 1800. These pulses targeted the midpoint between the inion and the mastoid, compared to only 300 pulses applied 2 centimetres beneath the inion by Gironell et al. in 2002.

Such findings also lend support to an emerging theory regardingthe cerebellum itself being centrally involved in the generation of ET and a presumed key target for rTMS.[1] Our findings contradicted the findings of Shin et al. in 2019 who found no improvement in either total or subscale FTM scores measured immediately after intervention and 4 weeks later, and Olfati, N. et al. in 2019 who found no significant improvement in overall FTM scores in rTMS compared to sham stimulation on day 5, day 12, or day 30 after application of a similar 1 Hz cerebellar rTMS.. That can be explained by the differences in the session numbers, the pulse numbers per session, and the coil sites between the present study and the two mentioned studies. Shin et al.[19] used a 5-session protocol with 1200 pulses per day implemented to the bilateral cerebellar hemispheres and the coil was positioned three centimeters lateral and one centimeter inferior to the inion, whereas Olfati, N. et al.[19] used a 5-session protocol with 900 pulses and the coil was positioned at 1/3 distance from the inion to the mastoid process.

The present results showed that the significant reduction in the FTM subscale C has lasted only for 1 month unlike the reduction in the FTM subscale A, subscale B, and total scale which has been lasting for 3 months. Parts A and B of the FTM tremor rating score indicate the severity of the tremor as determined by neurological examination, while part C is determined by an interview regarding how much the tremor impacted the patient's daily life.[15] The disparity in sub-scale responses to the active rTMS intervention suggests that reducing the severity of tremor as evaluated by neurological examination would not be enough to enhance patients' everyday functions. In the present study, there has been no significant difference in FTM subscore A, B, C, or total score of the sham group at day one, one month, two months, or three months after the sessions compared to the baseline score.

These results agree with the results revealed by Olfati, N. et al. in 2019,[19] Shin et al. in 2019,[18] and Gironell et al [16] in 2002 who reported no significant reduction in FTM subscore A, B, C, or total score after sham rTMS. A considerable, but not significant, fall in the FTM scores in the sham group degree noticed in day one indicating some placebo effect after sham rTMS. And that was also reported by Olfati, N. et al. in 2019 [19] and Shin et al. in 2019.[18] In this research, there has been no significant association between TRS-A, B, and C and total score and patient age or duration of tremors at baseline, day one, one month, two months, or three months after the sessions.

CONCLUSION

For patients suffering from severe essential tremor, cerebellar rTMS can be an effective therapy choice.

Conflict of interest : none

REFERENCES

1. Welton, T., Cardoso, F., Carr, J. A., Chan, L. L., Deuschl, G., et al. Essential tremor. - *Nat Rev Dis Prim*. 2021; 7(1), 1-17.
2. Louis, E. D., Rios, E., & Henchcliffe, C. How are we doing with the treatment of essential tremor (ET)? Persistence of patients with ET on medication: data from 528 patients in three settings. *Europ J Neurol*. 2010; 17(6), 882-4.
3. Zesiewicz, T. A., Shaw, J. D., Allison, K. G., Staffetti, J. S., Okun, M. S., et al. Update on treatment of essential tremor. *Curr Treat Option Neurol*. 2013; 15(4), 410-23.
4. Gironell, A., & Kulisevsky, J. Diagnosis and management of essential tremor and dystonic tremor. *Ther Adv Neurol Disord*. 2009; 2(4), 215-22.

5. Deuschl, G., Raethjen, J., Hellriegel, H., & Elble, R. Treatment of patients with essential tremor. *Lancet Neurol*. 2011; 10(2), 148-61.

6. Hedera P. Emerging strategies in the management of essential tremor. *Ther Adv Neurol Disord.* 2017; 10(2), 137–48.

7. Mohammed, N., Patra, D., & Nanda, A. A meta-analysis of outcomes and complications of magnetic resonance-guided focused ultrasound in the treatment of essential tremor. *Neurosurg Focus*. 2018; 44(2), E4.

8. Kang, N., & Cauraugh, J. H. Does non-invasive brain stimulation reduce essential tremor? A systematic review and meta-analysis. *PLoS One*. 2017; 12(9), e0185462.

9. Chalah, M. A., Lefaucheur, J. P., & Ayache, S. S. Non-Invasive central and peripheral stimulation: new hope for essential tremor?. *Front Neurosci*. 2015; 9, 440.

10. Obeso, Ignacio, Antonio Cerasa, and Aldo Quattrone. The effectiveness of transcranial brain stimulation in improving clinical signs of hyperkinetic movement disorders. *Front Neurosci.* 2016; 9. 486.

11. Helmich, R. C., Toni, I., Deuschl, G., & Bloem, B. R. The pathophysiology of essential tremor and Parkinson's tremor. *Curr Neurol Neurosci Rep*. 2013; 13(9), 1-10.

12. Raethjen, Jan, and Günther Deuschl. The oscillating central network of essential tremor. *Clin Neurophysiol.*. 2012; 123.1: 61-4.

13. Dupuis, M. J. M., Evrard, F. L., Jacquerye, P. G., Picard, G. R., & Lermen, O. G. Disappearance of essential tremor after stroke. *Mov Disord*. 2010; 25(16), 2884-7.

14. Bhatia, K. P., Bain, P., Bajaj, N., Elble, R. J., Hallett, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord*. 2018; 33(1), 75-87.

15. Fahn, Stanley, Eduardo Tolosa, and Concepcíon Marín. Clinical rating scale for tremor. *Parkin Dis Mov Disord.* 2. 1993; 271-80.

16. Gironell, A., Kulisevsky, J., Lorenzo, J., Barbanoj, M., Pascual-Sedano, B., et al. Transcranial magnetic stimulation of the cerebellum in essential tremor: a controlled study. *Arch Neurol*. 2002; 59(3), 413-7.

17. Popa, T., Russo, M., Vidailhet, M., Roze, E., Lehéricy, S., et al. Cerebellar rTMS stimulation may induce prolonged clinical benefits in essential tremor, and subjacent changes in functional connectivity: an open label trial. *Brain Stim*. 2013; 6(2), 175-9.

18. Shin, Hae-Won, Mark Hallett, and Young H. Sohn. Cerebellar repetitive transcranial magnetic stimulation for patients with essential tremor. *Parkin Dis Mov Disord.* 2019; 64: 304-7.

19. Olfati, N., Shoeibi, A., Abdollahian, E., Ahmadi, H., Hoseini, A., et al. Cerebellar repetitive transcranial magnetic stimulation (rTMS) for essential tremor: A double-blind, sham-controlled, crossover, add-on clinical trial. *Brain Stim* 2020; 13(1), 190-6.