CLINICAL RESPONSE TO HIGH FRQUENCYRTMS AMONG PATIENTS WITH CEREBRAL SMALL VESSEL DISEASE

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ABSTRACT:

Back Ground*: Cerebral small vessel disease (CSVD) is a condition of clinical and neuroimaging presentations that arise mainly from damage to the brain's small perforating vessels causing lacunar type strokes, Intracranial hemorrhage and insidious significant deficits in gait, urinary and cognitive domains which are progressive in nature rTMS showed efficacy regarding improving gait and cognition in subcortical pathologies as Multiple Sclerosis, Parkinson disease and vascular dementia. rTMS exerts efficacy through enhancing neuroplasticity and in part modulating associated neuronal inflammation.*

Aim of work: *Study the effect of High frequency rTMS on Cognitive symptoms among patients with cerebral small vessel disease with no acute stroke presentation.*

Patients and Methods: *40 patients are included, with MRI documented small vessel disease, symptomatic by either gait or cognitive or urinary symptoms or all. Randomized to 20 active and 20 sham groups, Active group received 6 sessions of high frequency Cz of intensity of 110% Motor Threshold. Sham group received 6 Sham sessions. Baseline line demographic data, vascular risk factors, radiological scales (Fazekas and Global cortical atrophy scale) were done to all patients, Baseline, post-sessions and 1 month follow up assesments were done regarding cognitive scales including FAB (Frontal assessment Battery) and Adam Brook scale.*

Results: *Comparing active group to sham group. Active rTMS has statistically significant improved FAB scores* ***(P < 0.001) and*** *Adam Brook scale scores* ***(P < 0.001)***

Conclusion*: our results suggested that High frequency Cz applied rTMS sessions showed statistically significant improvement in cognitive performance in patients with small vessel disease.*

Keywords: *Small vessel disease, TMS, Cognition,*

Role of researchers*: All authors contributed to the production for this manuscript. S.S was responsible for the field work.*

INTRODUCTION:

Cerebral small vessel disease (CSVD)' refers to a syndrome of clinical and imaging findings that are thought to result from pathologies in perforating cerebral arterioles, capillaries and venules. CSVD causes up to 45% of dementia, and accounts for about 20% of all stroke worldwide, 25% of ischaemic (or lacunar strokes), of whom about 20% are left disabled. Cognitive impairment, urinary and gait problems are also frequently seen in patients with CSVD and are difficult to treat and ameliorate(1).

The markers of SVD on magnetic resonance imaging (MRI) are white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMB) and enlarged perivascular spaces(3).These markers are

closely associated with increased mortality[4], poor physical function[5], stroke recurrence[6], cognitive decline[7] and depression[8].

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive and easily tolerated method that involve neuronal and glial-dependent mechanisms both of which have significance in the pathophysiology of various neurological diseases[9]. rTMS showed efficacy regarding improving gait in subcortical pathologies as MS and Parkinson disease, in addition enhancing symptoms in neurogenic incontinence and vascular dementia.

AIM OF WORK:

Study the effect of High frequency rTMS on Cognitive symptoms among patients with cerebral small vessel disease with no acute stroke presentation

PATIENTS AND METHODOLOGY:

Our Study is aninterventional randomized double blind study in which 40 patients were included based on the inclusion criteria mentioned below, recruited from Ain shams university hospital, Randomization occurred by sealed envelope method, in addition an informed consent was obtained from each patient with a detailed explanation of the nature and aim of the study and use and risks of rTMS.

The inclusion criteria of our study were an age limit of 45 years old or more, no gender preference, with MRI brain Suggestive of Small vessel disease in the form of deep white matter ischemia, Cerebral micro bleeds and enlarged Virchow spaces with no true diffusion restriction, presenting with cognitive complains in any related domain.

The study excluded any patient presented with acute or prior history of manifestation of acute ischemic or hemorrhagic stroke, whose Carotid duplex or MRA showed significant extracranial Carotid or intracranial significant stenosis and finally we excluded any patient who has absolute contraindication for rTMS sessions as Skull defects, Epilepsy, Skin scalp hematoma, Scalp infection, Deep brain stimulation or pacemaker device insertion.

The study measurements that are done to all the patients included; brain MRI with diffusion, FLAIR and MRA sequences to calculate baseline Fazekas score and the global cortical atrophy scale score, further work up included Hemoglobin A1C, full lipid profile, 12- lead ECG, echo and Carotid duplex. Cognitive scales included FAB scale and Adam Brook scale which are done to all the patients in the active and sham group at baseline, after rTMS sessions and at 4 weeks after the last session.

The included 40 patients were then randomized divided into 2 groups, active and sham group, each including 20 patients, Active group patients received high frequency rTMS sessions, 1000 Hz, on period is 10 seconds, off period is 20 seconds, intensity of 110 % of Motor threshold over CZ for 6 sessions every other day, while the sham group patients received the same protocol while using the sham coil.

RESULTS:

Demographic data, clinical characteristic and baseline assessment scales:

The demographics of the studied sample showed mean age of 65.7 years in active group and 63.6 years in sham group with male predominance of a ratio of 5:3, and a mean duration of illness of 2.67 years in active group and 2.45 years on sham group, Regarding the vascular risk factors for Small vessel disease in our sample, 62.5 % are hypertensive, 35 % are diabetics, 32.5 % are dyslipidemics, 32.5 % are smokers, 20 % are Ischemic heart disease, 15 % have

Peripheral arterial disease, 2.5 % (only one patient) had AF. Carotid duplex showed Intimal medial thickness of 1.32 mm in active, and 0.14 mm in sham group, with average Ejection fraction and Left atrial diameter in Echo study as shown in table (1).

Table (1): Demographic and vascular risk factors

		ACTIVE (NO.=20)		SHAM (NO.=20)		Chi /T Test	
		Frequency /Mean	Percentage / SD	Frequency / Mean	Percentage / SD	Chi / t	P
AGE		65.700	4.9535	63.650	7.9291	.981	.333
DURATION OF ILLNESS		2.6750	1.10352	2.4500	1.40394	.563	.576
GENDER	*MALE*	14	70%	10	50%	1.667	0.197
	FEMALE	6	30%	10	50%		
VASCULAR RF	Smoking	7	35%	6	30%	0.114	0.736
	HTN	10	50%	15	75%	2.667	0.102
	DM	7	35%	7	35%	0	1
	Hyperlipidemia	8	40%	5	25%	1.026	0.311
	ISHD	5	25%	3	15%	0.625	0.429
	PAD	3	15%	3	15%	0	1
	AFIB	1	5%	0	0%	0.311	1.026
Carotid IMT		1.320	.1399	1.285	.1424	.784	.438
ECHO	EF	61.800	6.3129	64.400	3.6620	-1.593	.119
	LAD	38.200	2.9308	37.600	2.8359	.658	.515
	SWAM	.150	.3663	.100	.3078	.467	.643

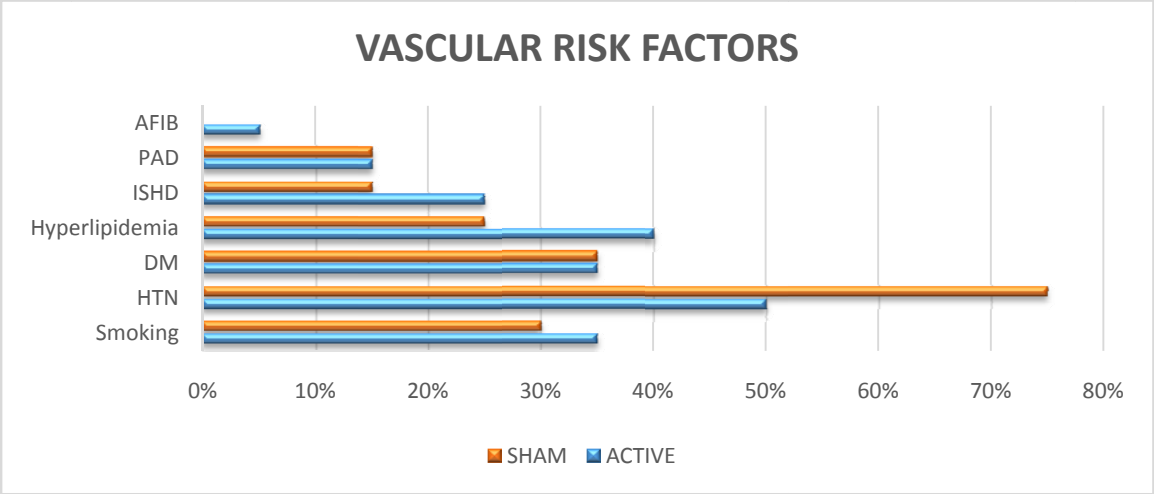

Diagram (1): Percentage of risk factors among active and sham groups

Baseline assessment for cognitive symptoms of the studied patients with small vessel disease showed homogenous sham and active groups with insignificant difference, Baseline cognitive assessment in our study showed lower than normal Frontal assessment battery (FAB) scores being 8.05 ± 3.9 in active group and 10.45 ± 3.54 in the sham group. In addition to lower than normal Adam Brook scale scores of 46.6 ± 18 in active group and 53.53 ± 12.3 among sham group as shown in table (3).

Table (2): Baseline cognitive scales.

Cognitive And Urinary Scales Baseline	ACTIVE		SHAM		T Test	
	Mean	SD	Mean	SD	t	P
FAB Total	8.05	3.94	10.45	3.5463	-2.025	0.05
ADAM BROOK Total	46.6	18.0216	53.55	12.3095	-1.424	0.164

The previously mentioned attenuated cognitive performance at baseline measurements was significantly related to the total Fazekas scale for white matter lesions, Higher Fazekas scale score is correlated to worse performance at baseline cognitive scales; (FAB: r:-0.527, P < 0.001 Adam Brook: r:-0.434, P=0.005), Baseline MRI based Global cortical atrophy (GCA) scale showed significant scores of 13.85 ± 9.49 in active group and 12.1 ± 6.406 in sham group, moreover GCA scale score is significantly correlated with baseline cognitive scales, with worse scales linked to more measured atrophy, as noticed when GCA scale is correlated with Adam Brook scale (r:-0.712, P < 0.001) *as in table (3)&(4)*

Table (3): Baseline regional and total global cortical atrophy scores

BRAIN IMAGING Baseline		ACTIVE		SHAM		T Test	
		Mean	SD	Mean	SD	T	P
FZ	*Periventricular*	2.700	.4702	2.550	.5104	.967	.340
	Deep White Matter Ischemia	2.700	.4702	2.550	.5104	.967	.340
	Total	5.400	.9403	5.100	1.0208	.967	.340
Total Global Cortical Atrophy Score		13.850	9.4939	12.100	6.4064	.683	.499

Table (4): Correlation between Baseline Fazekas score, baseline IL-1 and cognitive scales.

		FAB Total (T0)	Adden brook Total (T0)
Total brain atrophy	*Pearson*	-.425	-.639
	Sig	.006	.000
FZ Total	*Pearson*	-.527	-.434
	Sig	.000	.005

Post rTMS data showed improvement regarding cognitive symptoms. The improvement regarding the gait scales is demonstrated as statistically significant difference in the measured cognitive scales, T1-T0 assessment showed **2.4** point increase in FAB scores **(Pless than 0.001),2.1** point increase in Adam Brook scale scores **(P less than 0.001),** furthermore, the T2- T0 assessment showed persistent but lesser difference, of 1 point in FAB scale score **(P less than 0.001)** and 1.1 points in Adam Brook scale score **(P= 0.005)** ***as shown in table (5)and diagram (2)***

Active vs sham assessment scales across 3 time points:

Table (5): Cognitive assessment scales in Active versus Sham groups.

	ACTIVE		SHAM		T TEST	
	mean	SD	mean	SD	T	P
FAB (T1-T0)	2.4000	1.14248	.1500	.36635	8.387	.000
ADDENBROOK (T1-T0)	2.1000	1.48324	-.2500	3.32257	2.888	.006

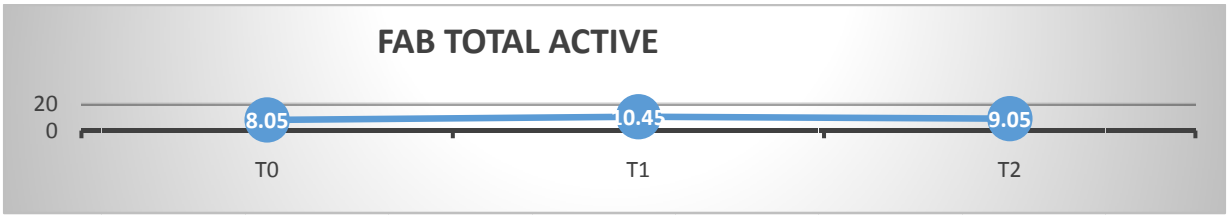

Diagram (2): FAB scores in active TMS groups across T0, T1 and T2 follow up points.

DISCUSSION

The demographics of the studied sample showed mean age of 65.7 years in active group and 63.6 years in sham group with male predominance of a ratio of 5:3, and a mean duration of illness of 2.67 years in active group and 2.45 years on sham group, The data is matching with ***Esther M.C et al.,2017***[10], work using the RUN DMC cohort study, including 59.1 % males, Mean age of 62.5 +/- 7.7 years.

Baseline assessment for cognitive symptoms of the studied patients with small vessel disease showed homogenous sham and active groups with insignificant difference,The measured attenuated cognitive performance at baseline measurements were significantly related to the total Fazekas scale for white matter lesions, Higher Fazekas scale score and consequently White matter hyper intensities (WMH) burden were correlated to worse performance at baseline cognitive scales; (**FAB: r:-0.527, P less than 0.001 Adam Brook: r:-0.434, P=0.005**), This data comes along the available literature highlighting the above mentioned relation between ***(Xiaopei Xu et al.,2018)***[11]

Post interventional data after high frequency rTMS sessions showed improvement regarding cognitive symptoms, T1-T0 assessment showed **2.4** point increase in FAB scores **(Pless than 0.001), 2.1** point increase in Adam Brook scale scores **(P less than 0.001),** furthermore, the T2- T0 assessment showed persistent but lesser difference, of 1 point in FAB scale score **(P less than 0.001)** and 1.1 points in Adam Brook scale score **(P= 0.005).**This comes in the same line with ***GuseB.et al., 2010***[12]systematic review summarizing 30 studies which entitled the cognitive enhancing effect of Hf- rTMS sessions over Left DLPFC in various pathologies including depressions, PD and post-stroke patients.

Summary:

This study demonstrated that High frequency Cz applied rTMS sessions for at least 6 sessions showed statistically significant improvement in cognitive performance if compared to sham treatment in a group of 40 patients with small vessel disease.

Recommendations:

Our study recommends that high frequency TMS at Cz region can be added as an adjuvant tool in the cognitive rehabilitation plan for patients with small vessel disease presenting with disabling cognitive symptoms in addition to pharmacological agents, antiplatelet therapy and risk factors control

In addition further studies are needed to correlate regional cortical atrophy to different domains in cognitive performance in patients with SVD and possible application of targeted TMS or related neuro-modulatory tools which can be tailored according to each patient's profile and needs. Further data should be collected about the possible role of TMS in reducing the other domains of small vessel disease.

The limitations of the study includedthe small sample size, so that the

results could not be generalized. Being not a well-representative community sample, as the sample was collected from Ain Shams University hospital only, another limitation is the use of one rTMS technique and the use of limited number of scales to assess cognitive affection, Finally the use of performer dependent visual rating for Fazekas and the Global Cortical Atrophy scales as assessment tools.

Declaration

All authors have no conflict of interest.

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الاستجابة الاكلينيكيةلاستخدامجلسات التنبيه المغناطيسي المتكرر عبر الجمجمة عالي التردد فى مرضى قصور الأوعية الدموية المخية الدقيقة

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الملخص العربى

المقدمة: ان مرض قصورالأوعية الدموية الدماغية الدقيقة هو حالة من العروض السريرية والتصوير العصبي التي تنشأ أساسا من الأضرار التي تلحق بالأوعية الدمويةالدقيقةمسببة السكتات الدماغية ذات الحجم الصغيرة ، نزيف داخل الجمجم وعجز كبيربطئ التقدم في مجالات التحكم البولي و القدرات الإدراكية و الحركة . أظهراستخدامجلسات التنبيه المغناطيسي المتكرر عبر الجمجمة) (rTMSفعالية فيما يتعلق بتحسين المشي والإدراكفي امراض كالتصلب المتناثر و مرض الشلل الرعاش و الخرف الوعائي

تاتى فعالية جلسات التنبيه المغناطيسي المتكرر عبر الجمجمة (rTMS) من خلال تعزيز المرونة العصبية وتعديل الالتهاب العصبي .

الغرض من الدراسة :دراسة تأثير جلسات التنبيه المغناطيسي المتكرر عبر الجمجمةrTMSعالية التردد على الأعراض المعرفية بين المرضى الذين يعانون من مرض قصور الأوعية الدموية الدماغية الدقيقة مع عدم وجود أعراض السكتة الدماغية الحادة.

طريقة الدراسة:يتم تضمين 40 مريضا ، مع رنين مغناطيسى موثق مرض قصور الأوعية الدموية الدماغية الدقيقة مع عدم وجود أعراض السكتة الدماغية الحادة و وجود أعراض قصور التحكم البولي و القدرات الإدراكية و الحركة . تم اختيارهم بشكل عشوائي إلى ٢٠ مجموعة نشطة و ٢٠ مجموعة صورية، تلقت المجموعة النشطة ٦ جلسات ذات تردد عالي من جلسات التنبيه المغناطيسي المتكرر عبر الجمجمة و تلقت المجموعة الصورية ٦ جلسات من التنبيه المغناطيسي المتكرر عبر الجمجمة الصورية. تم إجراء البيانات الديموغرافية وعوامل الخطر الوعائية والمقاييس الإشعاعية (مقياس Fazekas والضمور القشري العالمي) لجميع المرضى ، وتم إجراء تقييم أساسي بعد الجلسات وبعد متابعة شهر واحد اختبار تقييم الفص الامامى المعرفي اختبار آدم بروك المعرفي

النتائج: بمقارنة المجموعة النشطة لمجموعة الشام الصورية تسببت ٦ جلسات من التنبيه المغناطيسي المتكرر عبر الجمجمةعالية التردد rTMS تحسناملحوظاذات دلالة إحصائية في مقاييس القدرات المعرفية فى مرضى قصور الأوعية الدموية الدماغية الدقيقة (قيمة**P**أقل من **0.001**)

الخاتمة:النتائج التي توصلنا إليها تشير إلى أن استخدام التنبيه المغناطيسي المتكرر عبر الجمجمةعالية التردد rTMSأظهر تحسنا ملحوظا القدرات المعرفية فى مرضى قصورالأوعية الدموية الدماغية الدقيقة