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Relationship Between Baseline Upper Limb Motor Impairment Level and Motor Gain in Chronic Stroke Patients Treated with Repetitive Transcranial Magnetic Stimulation as an Adjunct to Conventional Rehabilitation

Geleneksel Rehabilitasyona Ek Olarak Repetetif Transkraniyal Manyetik Stimülasyon ile Tedavi Edilen Kronik İnmeli Hastalarda Tedavi Öncesi Üst Ekstremite Motor Bozukluk Düzeyi ile Motor Kazanım Arasındaki İlişki

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This study was prepared based on the findings of Nazrin AGHAZADA's thesis study titled "The relationship between the pre-treatment upper extremity motor impairment level and motor gain in chronic stroke patients treated with inhibitory repetitive transcranial magnetic stimulation in addition to conventional rehabilitation" (İzmir: İzmir Kâtip Çelebi University; 2024).

ABSTRACT Objective: To investigate the relationship between baseline upper limb motor impairment level and motor gain in chronic stroke patients treated with low frequency repetitive transcranial magnetic stimulation (LF-rTMS) and conventional rehabilitation. **Material and Methods:** In this retrospective study, 48 chronic stroke patients were divided into 3 subgroups according to the baseline Fugl-Meyer Upper Extremity Motor Impairment Scale (FM-UL) scores: severe (n=16), severe-to-moderate (n=15), and moderate-to-mild (n=17). The groups were compared for motor gain (change in the FM-UL). **Results:** The administration of 10 sessions of LF-rTMS treatment (a total of 12,000 pulses at 90% of resting motor threshold) immediately prior to conventional rehabilitation resulted in statistically significant motor gains at all levels of upper limb motor impairment, from severe to moderate-to-mild [median motor gains (interquartile range) were 0.0 (0.0 to 1.0), p=0.014; 2.0 (1.0 to 3.75), p=0.002; and 2.0 (0.0 to 4.50), p=0.006, respectively]. There was also a statistically significant difference in motor gain between the groups (p=0.027). Median motor gains in the severe-to-moderate and moderate-to-mild groups were significantly larger than those in the severe group (adjusted p-values were <0.05). **Conclusion:** The results of this study suggest that LF-rTMS followed by conventional rehabilitation may contribute to upper limb motor recovery in chronic stroke patients, regardless of the level of upper limb motor impairment. However, whether the LF-rTMS has a clinically meaningful effect in isolation should be investigated in robust randomised controlled trials stratifying subjects according to their baseline level of upper limb motor impairment.

Keywords: Chronic stroke; upper limb motor impairment level; low frequency repetitive transcranial magnetic stimulation; motor gain

ÖZET Amaç: Düşük frekanslı repetetif transkraniyal manyetik stimülasyon [low frequency repetitive transcranial magnetic stimulation (LF-rTMS)] ve geleneksel rehabilitasyon ile birlikte tedavi edilen kronik inmeli hastalarda tedavi öncesi üst ekstremite motor bozukluk düzeyi ile motor kazanım arasındaki ilişkiyi araştırmak. **Gereç ve Yöntemler:** Bu retrospektif çalışmada, 48 kronik inme hastası başlangıçtaki Fugl-Meyer Üst Ekstremite Motor Bozukluk Ölçeği [Fugl-Meyer Upper Extremity Motor Impairment Scale (FM-UL)] skorlarına göre ağır (n=16), ağır-orta (n=15) ve orta-hafif (n=17) olmak üzere 3 alt gruba ayrıldı. Ardından, gruplar motor kazanım (FM-UL'deki değişim) açısından karşılaştırıldı. **Bulgular:** Konvansiyonel rehabilitasyondan hemen önce 10 seans LF-rTMS tedavisi (istirahat motor eşiğinin %90'ında toplam 12.000 atım) uygulanması, üst ekstremite motor bozukluğunun ağırdan orta-hafife kadar tüm seviyelerinde istatistiksel olarak anlamlı motor kazanımla sonuçlandı [medyan motor kazanım (çeyrekler arası aralık) ağırdan orta-hafif motor bozukluk düzeyine doğru sırasıyla 0,0 (0,0 ila 1,0), p=0,014; 2,0 (1,0 ila 3,75), p=0,002 ve 2,0 (0,0 ila 4,50), p=0,006]. Gruplar arasında motor kazanım açısından istatistiksel olarak anlamlı fark vardı (p=0,027). Şiddetli-orta ve orta-hafif gruplardaki medyan motor kazanımlar şiddetli gruptakilerden istatistiksel anlamlı olarak daha fazlaydı (düzeltilmiş p değerleri <0,05). **Sonuç:** Bu çalışmanın sonuçları, geleneksel rehabilitasyonun ardından uygulanan LF-rTMS'nin, üst ekstremite motor bozukluk düzeyinden bağımsız olarak kronik inme hastalarında üst ekstremite motor iyileşmesine katkıda bulunabileceğini göstermektedir. Bununla birlikte, LF-rTMS'nin tek başına klinik olarak anlamlı bir etkiye sahip olup olmadığı, inme hastalarını başlangıçtaki üst ekstremite motor bozukluk düzeylerine göre sınıflandıran sağlam randomize kontrollü çalışmalarla araştırılmalıdır.

Anahtar Kelimeler: Kronik inme; üst ekstremite motor bozukluk düzeyi; düşük frekanslı repetetif transkraniyal manyetik stimülasyon; motor kazanım

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It is crucial to promote and sustain recovery through neurorehabilitation practices aimed at inducing neuroplastic changes, as spontaneous neurological recovery is insufficient for a significant proportion of stroke survivors.[1] However, traditional and/or task-specific rehabilitation methods may not be sufficient to induce and maintain adaptive neuroplasticity and suppress the development of maladaptive neuroplasticity. Therefore, additional effective and safe non-invasive treatment methods are needed to improve motor performance and skills. Among these methods, transcranial magnetic stimulation (TMS) is often used as an adjunctive treatment tool in stroke rehabilitation, alongside various other rehabilitation approaches.

Repetitive TMS (rTMS) is one of the TMS techniques that can be used for therapeutic purposes because its effects on cortical activity last beyond the stimulation period.[2] The effect of rTMS on cortical neurons varies depending on the frequency applied; frequencies of 1 Hz and below have an inhibitory effect, while frequencies of 5 Hz and above have a facilitatory effect.[3] Inhibitory (≤1 Hz-low-frequency) rTMS (LF-rTMS) is used to suppress the intact brain side to increase the activity of the lesioned side by altering the balance of interhemispheric inhibition, which is one of the proposed mechanisms of motor recovery in stroke.[3,4]

Motor recovery in stroke survivors is determined by many interacting factors. The initial level of motor impairment and the time since the stroke are among the important factors affecting motor recovery.[5] The literature regarding the effect of LF-rTMS treatment on upper limb motor impairment in chronic stroke patients is inconsistent.[6-18] Several studies have suggested that LF-rTMS may be effective in upper limb motor recovery when added to rehabilitation interventions in chronic stroke patients, even in those with severe upper limb motor impairment.[6-9,15,17,18] On the other hand, some others have suggested that LF-rTMS does not provide an additional benefit to rehabilitation practices in chronic stroke patients with severe to mild upper limb motor impairment.[10-14,16] This retrospective study aimed to investigate whether the motor gain achieved with LF-rTMS plus conventional rehabilitation differed depending on the baseline (pre-treatment) motor impairment level of the affected paretic upper limb in chronic stroke patients.

MATERIAL AND METHODS

STUDY DESIGN, DATA SOURCE, AND ETHICAL APPROVAL

This retrospective study used data from stroke patients treated with LF-rTMS in a single centre. The stroke patients whose data were used in the present study were volunteers who had previously taken part in prospective studies carried out at the centre. Data captured were demographic characteristics including age and sex and clinical characteristics including time since stroke, affected side, dominant side, lesion type and location, and Fugl-Meyer Upper Limb Impairment Scale (FM-UL) scores. The LF-rTMS parameters captured were intensity of stimulation, stimulation duration, number of stimuli, cumulative number of stimuli, and number of sessions. The study started after local ethics committee approval (İzmir Kâtip Çelebi University Faculty of Medicine Non-interventional Clinical Research Ethics Committee, date: September 21, 2023, no: 0364). Written informed consent was not required because of the retrospective nature of the study. However, the patients whose data were used were those who had participated in previous scientific studies conducted at the centre and who had given their written informed consent that their data to be used for research purposes in the studies in which they participated and in future studies. The study was conducted in accordance with the principles of the Declaration of Helsinki.

STUDY POPULATION

Patients were included if they were ≥18 years of age, had a first-ever stroke, had at least 6 months between stroke diagnosis and LF-rTMS treatment, received at least 5 sessions of LF-rTMS to the contralesional primary motor cortex, and had both pre- and post-treatment FM-UL data. Patients were excluded if they were under 18 years of age, had bilateral hemiparesis, had a history of more than one stroke, had no upper limb motor impairment, received rTMS to the ipsilesional cortex, and did not have at least one of the pre- or post-treatment FM-UL scale score.

The patients included were categorized into four groups based on their pre-treatment FM-UL scores: severe (0 to 15), severe-to-moderate (16 to 34), moderate-to-mild (35 to 53), and mild (54 to 66).[19]

INTERVENTIONS

Conventional Rehabilitation

An individualized rehabilitation program was implemented based on the clinical characteristics of each stroke patient. The program included in-bed exercises, range of motion exercises, stretching exercises, strengthening exercises, occupational therapy, ambulation-balance exercises, exercises to improve posture, and activities of daily living.

LF-rTMS

The LF-rTMS was applied to the intact primary motor cortex to reduce its inhibitory effect on the lesioned hemisphere. The participants underwent the application while seated in a comfortable armchair with armrests and head support. Both hands rested comfortably on their upper thighs. Before each session, visual or electromyography recordings were taken to determine the resting motor threshold.

OUTCOME MEASURE

The primary endpoint was the change score (motor gain) in the FM-UL at the post-treatment time point compared to the baseline (pre-treatment). The FM-UL scale consists of four subsections (shoulder-arm, wrist, hand, and coordination-speed) and was developed to measure motor impairment from proximal to distal and from synergy to isolated voluntary movement.[20,21] Scoring is based on direct observation of performance. The scale assigns a score between 0 and 2 to each item based on the patient's motor performance. A higher score indicates better performance. The maximum score for upper extremity motor performance is 66.[20,21]

STATISTICAL ANALYSIS

Data analysis was performed using MedCalc® statistical software version 22.021 (MedCalc Software Ltd, Ostend, Belgium). Demographic and clinical characteristics are presented as number (percentage) and median (range or 25th-75th percentiles) for the categorical and numerical variables, respectively. The chi-square test for categorical variables and the Kruskal-Wallis test for numerical variables were used to compare baseline characteristics between the groups. The Wilcoxon test was used for within-group comparison of the FM-UL over time. The groups were compared for motor gain with the Kruskal-Wallis test. If the Kruskal-Wallis test result was significant, the Conover test was used for post hoc analysis. The statistical significance level was set at 0.05 or below.

RESULTS

BASELINE CHARACTERISTICS

The study evaluated the data of 193 stroke patients who received rTMS treatment before August 2023. Out of 193 patients, 51 stroke patients (34 males and 17 females, with a median age of 62 years) who met the inclusion/exclusion criteria were included in the study. The LF-rTMS treatment parameters were consistent across all patients. The stimulation intensity was set at 90% of the resting motor threshold value, with each session lasting 20 minutes. A total of 10 sessions were administered, with 1,200 pulses per session and a cumulative total of 12,000 pulses.

In 26 (51%) patients, information on the location of the lesion could be obtained. Of these 26 patients, 16 had subcortical lesions, 6 had cortical lesions and 4 had both cortical and subcortical lesions.

The severe group consisted of 16 patients, the severe-to-moderate group had 15 patients, and the moderate-to-mild group had 17 patients. Due to the insufficient number of patients in the mild group (n=3), statistical analysis was not performed on this group, and the mild group was excluded from group comparisons. The groups were not similar in terms of gender (p=0.025). The percentage of male patients in the severe group was significantly lower (43.8%) than that in the other groups (86.7% in the severe-to-moderate group and 76.5% in the moderate-to-mild group). Analyze for lesion location was not considered appropriate due to significant missing data. However, it was clear that the study population was heterogeneous in terms of lesion location. The comparison of the groups for demographic and clinical characteristics at baseline is displayed in Table 1.

TABLE 1: Demographic and baseline clinical characteristics of the patients by groups.

	Total, n=48	Severe, n=16	Severe-to-moderate, n=15	Moderate-to-mild, n=17	p‡
Age, year	62 (33 to 76)	64.5 (45 to 76)	56 (33 to 70)	62 (45 to 70)	0.285
Sex, male, n (%)	33 (68.7)	7 (43.8)	13 (86.7)	13 (76.5)	0.025
Time since stroke, month	15 (6 to 64)	16 (6 to 48)	15 (7 to 64)	13 (7 to 32)	0.804
Affected side, right, n (%)	27 (56.2)	6 (37.5)	8 (53.3)	13 (76.5)	0.076
Dominant side, right, n (%)	39 (81.2)	11 (68.7)	12 (80)	16 (94.1)	0.173
Lesion type, ischemic, n (%)	42 (87.5)	14 (87.5)	14 (93.3)	14 (82.4)	0.645
FM-UL, total	20.5 (0 to 52)	7 (0 to 14)	20 (16 to 32)	43 (36 to 52)	<0.001

‡The Kruskal-Wallis test; Numerical data are given as median (minimum, maximum). FM-UL: Fugl-Meyer Upper Limb Motor Impairment Scale.

TABLE 2: Comparison of the motor gains (change in the FM-UL) by groups.

	Pre-treatment	Post-treatment	Δ FM-UL	p*
Severe (n=16)	7.0 (4.0 to 9.5)	7.0 (4.5 to 9.5)	0.0 (0.0 to 1.0)	0.014
Severe-to-moderate (n=15)	20.0 (17.0 to 26.5)	22.0 (19.5 to 32.25)	2.0 (1.0 to 3.75)‡	0.002
Moderate-to-mild (n=17)	43.0 (38.0 to 46.5)	48.0 (40.75 to 50.25)	2.0 (0.0 to 4.5)‡	0.006
Total (n=48)	20.5 (9.5 to 38.5)	22.5 (9.5 to 41.5)	1.0 (0.0 to 3.0)	<0.001
p†			0.027	

*The Wilcoxon test; †The Kruskal-Wallis test; ‡When the Kruskal-Wallis test result was significant, post hoc analysis was performed using the Conover test. The median change in both the severe-to-moderate group and the moderate-to-mild group were larger than those in the severe group (adjusted p values <0.05, the average ranks were 16.97, 28.77, and 27.82 for the severe, severe-to-moderate, and moderate-to-mild groups, respectively). The data are presented as median (25^{th} to 75^{th} percentiles).
FM-UL: Fugl-Meyer Upper Limb Motor Impairment Scale.

PRIMARY OUTCOME

The Wilcoxon test showed a significant motor improvement in all three groups. Furthermore, the Kruskal-Wallis test indicated a statistically significant difference between the groups in terms of motor gain (p=0.027). The post hoc analysis revealed that median motor gain in the severe-to-moderate and moderate-to-mild groups was significantly higher than those in the severe group (adjusted p values p<0.05) (Table 2).

DISCUSSION

This study investigated the relationship between baseline (pre-treatment) motor impairment level and motor gain obtained with contralesional LF-rTMS treatment followed by conventional rehabilitation in chronic stroke patients. The results have indicated that administering 10 sessions of LF-rTMS treatment (a total of 12,000 pulses at 90% of resting motor threshold) immediately before conventional rehabilitation led to statistically significant motor gain at all levels of upper limb motor impairment, from severe to moderate-to-mild.

The efficacy/effectiveness of rTMS in chronic stroke patients has been studied extensively. However, few studies have focused directly on whether motor gain differs according to the level of baseline upper limb motor impairment.[9,22,23] Yukawa et al. divided 40 chronic stroke patients into two groups as severe and mild, based on Brunnstrom's hand motor recovery stages.[22] After 12 sessions of LF-rTMS followed by occupational therapy, a statistically significant improvement in the FM-UL was found in the mild group, but not in the severe group.[22] In a recently published retrospective cohort study with a large sample size, the study population was divided into three subgroups as severe (≤20), moderate (21-45), and mild (≥46) according to the pre-treatment FM-UL scores.[23] The combined effect of rTMS and occupational therapy was statistically significant in all groups, with a trend of decrease from severe to mild.[23] In another recent retrospective cohort study, chronic stroke patients were stratified into 5 strata as

no (<23), poor (≥23-<32), limited (≥32-<42), notable (≥42-<53), and full (≥53) according to FM-UL scores at 6 months post-stroke.[9] There was statistically significant motor gain in all groups of motor impairment levels from low to high with no significant association between baseline motor impairment level and motor gain.[9] Regardless of whether the subgroups were more homogeneous or heterogeneous in terms of baseline level of upper limb motor impairment, the common aspect of the studies in the literature, including the current study, is that significant motor gains were achieved with LF-rTMS added to upper limb rehabilitation.[9,23] However, due to the study designs, it is not possible to comment on the isolated effect of LF-rTMS therapy based on the results of these studies, including the present one. In a randomised controlled trial investigating the efficacy of LF-rTMS in chronic stroke patients with moderate to mild motor impairment (to our knowledge the most methodologically sound study in this field), LF-rTMS treatment was found to be ineffective.[9,12,23] In another randomised controlled clinical trial conducted in chronic stroke patients with severe motor impairment, LF-rTMS treatment has been found to be statistically effective, but the clinical value of motor gain achieved with active LF-rTMS has remained controversial.[17]

Although the importance of clinically relevant improvement in motor performance has been noted in the literature, the interpretation of the results obtained in terms of clinical significance has generally been overlooked. Furthermore, the extent to which a change in FM-UL is considered clinically significant is a matter of debate. A 4.25-to 7.5-point change in the FM-UL in chronic stroke patients with severe to moderate motor impairment has been suggested as a minimum clinically important difference.[24] Considering the 4.25-point chance as the threshold for clinically important improvement, the combination of LF-rTMS and occupational therapy appears to have a clinically relevant treatment effect.[9,23] However, in stroke patients with severe motor impairment, an increase of 4.25 to 7.5 points may not be sufficient to perceive the change that occurs with treatment by a patient. Hiragami et al. calculated the minimum clinically important difference in total FM-UL to be 12.4 points in stroke patients with severe to moderate motor impairment.[25] If at least 12.4-point chance is considered as the threshold for clinically important improvement, the combination of LF-rTMS and occupational rehabilitation appears to be clinically irrelevant.[9,23] None of the groups based on the motor impairment level reached these two threshold values with the treatment in the current study. The small sample size, differences in the characteristics of the study populations, and differences in stimulation parameters may have led to divergent results.

This study has a restriction regarding the LF-rTMS parameters used. All patients were exposed to the same LF-rTMS parameters (a total of 12,000 pulses at 90% of the resting motor threshold). Because stimulation parameters can influence the effect of LF-rTMS, the results should be interpreted specifically for these parameters used.[26] However, it is still controversial what the optimal parameters are. The present study has also some limitations. The study had a retrospective design without a control group. In this respect, it was not possible to reveal the isolated effect of rTMS. The sample consisted of patients from a single center and was relatively small. Additionally, there was not enough patient clustering in the mild motor impairment group. Although stroke patients in the chronic phase were included in the study, the range of stroke duration was quite wide. The study population was also heterogeneous in terms of lesion location. Lastly, although more homogeneous groups were tried to be created according to the baseline FM-UL scores, the homogeneity within the groups may not have been sufficient.

CONCLUSION

The LF-rTMS followed by conventional rehabilitation may contribute to upper limb motor recovery in chronic stroke patients, regardless of the level of upper limb motor impairment. However, due to the study design, nothing can be said about the isolated effect of LF-rTMS. Additionally, the motor gains achieved did not reach a clinically significant level across all levels of motor impairment. Whether the LF-rTMS has a clinically meaningful effect in isolation should be investigated in robust randomised controlled trials stratifying subjects according to their baseline level of upper limb motor impairment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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