JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2017; 2: 29-35
DOI: 10.5152/jbachs.2017.110

Original Article

The Effects of Navigated Repetitive Transcranial Magnetic Simulation and Brunnstrom Movement Therapy on Upper Extremity Proprioceptive Sense and Spasticity in Stroke Patients: A Double-Blind Randomized Trial

Mehmet Özkeskin[1], Vesile Öztürk[2], Raif Çakmur[2], Bilge Kara[3], Fadime Küçük[4]

[1]Department of Physical Therapy and Rehabilitation, Dokuz Eylül University Institute of Health Sciences, İzmir, Turkey
[2]Department of Neurology, Dokuz Eylül University School of Medicine, İzmir, Turkey
[3]Department of Neurological Physiotherapy and Rehabilitation, Dokuz Eylül University School of Physical Therapy and Rehabilitation, İzmir, Turkey
[4]Department of Physical Therapy and Rehabilitation, Hacettepe University Institute of Health Sciences, Ankara, Turkey

Address for Correspondence: Mehmet Özkeskin **E-mail:** mehmet.ozkeskin76@gmail.com
Received: 30.12.2016; **Accepted:** 28.02.2017; **Available Online Date:** 18.04.2017

Cite this article as: Özkeskin M, Öztürk V, Çakmur R, Kara B, Küçük F. The Effects of Navigated Repetitive Transcranial Magnetic Simulation and Brunnstrom Movement Therapy on Upper Extremity Proprioceptive Sense and Spasticity in Stroke Patients: A Double-Blind Randomized Trial. J Basic Clin Health Sci 2017; 2: 29-35

Abstract

Purpose: The purpose of this study is to investigate the effects of various treatments (repetitive transcranial magnetic stimulation and Brunnstrom movement therapy) on upper extremity proprioceptive sense and spasticity.

Methods: Twenty-one stroke patients were included in the study. The treatment group (Group I; n=10) was administered navigated real repetitive transcranial magnetic stimulation (rTMS), and the control group (Group 2; n=11) was administered sham rTMS by the first researcher. The patients in both groups had upper extremity exercises according to Brunnstrom movement therapy (BMT). The patients were assessed using the Brunnstrom recovery stages (BRS), proprioceptive sense assessment, and the modified Ashworth scale (MAS).

Results: Between the treatment group and control group patients, there were no significant statistical differences obtained from pre-treatment and postreatment tenth day, first month, and third month by BRS wrist, hand, and upper extremity stages. The intragroup comparison of the treatment group patients revealed a statistically significant difference between the pre-treatment and post-treatment third month BRS-hand and BRS-upper extremity stages.The pretreatment and postreatment tenth day and first month evaluations of the wrist proprioceptive sense of the groups presented a significant difference. There was no statistically significant difference between the groups in terms of MAS scores before and after treatment evaluations.

Conclusion: The rTMS and BMT approaches that were implemented in the study affected the proprioceptive sense of the wrist after the treatment and in the early period but did not change spasticity.

Keywords: Repetitive transcranial magnetic stimulation, stroke, Brunnstrom recovery stages, proprioceptive sense, spasticity

INTRODUCTION

Proprioceptive sense is the individual's ability to perceive the position and the motion of his/her body segments in the space via somatosensorial impulses sent by the receptors in the skin, muscles, and joints (1). Researchers have stated that the proprioceptive sense, which is the awareness sense of the body, consists of three fundamental senses: kinesthesia, joint position sense, and neuromuscular control (2). The proprioceptive sense plays a crucial role in carrying out and controlling daily activities, maintaining posture and balance, joint stability, and motor learning (3, 4). Neuromuscular control is affected by proprioceptive inefficiencies apart from motor dysfunctions. It has been shown that proprioceptive knowledge is of extreme importance for the neural control of motion and that the upper extremity proprioceptive sense is commonly decreased or evanished following stroke (5). It has been explained that the proprioceptive deficit incidence rate is 50-65% in stroke patients, which affects daily activities and quality of life negatively (6, 7). It has been stated that proprioceptive and motor deficits have different recovery rates in the first six months following stroke (8). In stroke patients, sensorimotor learning calls for a sound somatosensorial impulse, which is possible through sensorimotor rehabilitation (9). The Bobath, Brunnstrom, Johnstone, and Rood proprioceptive neuromuscular facilitation techniques and the motor learning method, commonly utilized by physiotherapists, are based upon treating sensorimotor functions (10). There exist several recent studies that report that the pain-free, non-invasive transcranial magnetic stimulation (rTMS) application decreases spasticity or that it has no effect (11-13). Stroke rehabilitation is provided by decreasing the transcallosal inhibition from the unaffected motor cortex to

the affected motor cortex via 1 Hz rTMS applied on the motor cortex (14, 15). Whereas there is a limited number of studies in the literature with various results on the effects of rTMS and physiotherapy combination on spasticity, a study dealing with the effect of rTMS and physiotherapy combination on proprioceptive sense has not been found. This study was planned to investigate the effect of rTMS and Brunnstrom movement therapy (BMT) on upper extremity proprioceptive sense and spasticity (11, 12).

METHODS

Patients

Twenty-one stroke patients in the age range of 18 to 90 years were enrolled in this study. The inclusion criteria were the following: first time unilateral ischemic stroke, >1 month after the onset of stroke, Brunnstrom stage 2-6 for affected hand and upper extremity, muscle tone at the wrist with a modified Ashworth scale (MAS) score >1+, and no cognitive impairment (a pre-treatment SMMT score of >26). The exclusion criteria were hemorrhagic stroke patients, patients who used antispasticity drugs within 6 months before treatment, history of seizure, and patients with pathological conditions referred to as contraindications for rTMS in the guidelines suggested by Wasserman (16). Sixty-six of the 87 patients enrolled in the study were excluded from the study due to reasons such as a history of epilepsy, multiple strokes, advanced cancer stages, or cardiac pacemaker. Participants were randomized by means of a 1:1 allocation. Allocations were stored in sealed, numbered envelopes and opened only at the time of recruitment.

Study Design

The study was a randomized, double-blind, sham-controlled study. In the course of the study, treatment of the patients was performed by the first researcher while the evaluation of the patients was carried out by the second researcher, who was blind to navigated rTMS. The patients were not informed about whether the rTMS was real or sham.

The treatment group (Group 1) was administered (n=10) navigated real rTMS (25 min) plus BMT (45 min) by the first researcher, and the control group (Group 2) was administered (n=11) sham rTMS (25 min) plus BMT (45 min). All treatments were performed for a total of 10 days (a five-day implementation, two days off, five-day implementation). All subjects were instructed in do-it-yourself exercises and given a home program.

Application of Navigated rTMS

Prior to the rTMS, all patients underwent a 3D-TI compatible magnetic resonance imaging (MRI) study. The individual brain MRI was then utilized in the navigation software. Navigated rTMS was performed using the Nexstim eXimia TMS stimulator guided by eXimia Navigated Brain Stimulation (NBS) image-guidance system (navigation software version 3.2.2) (Nextim; Eximia, Helsinki, Finland). During the sessions, the patient was seated on a comfortable chair. The patientreceived rTMS over the hand area of the primary motor cortex in the unaffected hemisphere determined with navigation by the first researcher in the TMS laboratory after their resting motor thresholds (rMT) were detected (MagPro X100; Medtronic, Dusseldorf, Germany). The rMT was determined in each patient once before treatment and was defined as the minimum stimulus intensity able to elicit. The optimal site of stimulation on the skull was defined as the location where the largest motor evoked potentials (MEPs). MEPs were recorded in a belly-tendon (respectively, cathode-anode) montage on the skin overlying the first dorsal interosseal muscle of the unaffected hand. The patients were delivered 1 Hz rTMS at 90% of rMT for 25 min with the TMS device (1500 pulses). In each treatment session, 1500 pulses of 1 Hz rTMS were applied to the motor cortex in the unaffected hemisphere. Dosing parameters were based on previous studies. Navigated rTMS application was conducted for five consecutive days, and then it was suspended for two days and conducted for another five consecutive days. Sham stimulation was performed with a coil that imitated the sound of a real TMS coil. The stimulation parameters were chosen in accordance with the current safety guidelines for rTMS (16). The patientsin the control group underwent the same application provided by the other researcher for 10 days except that they were delivered sham rTMS, not real rTMS. The patient in both groups had BMT (45 min) provided by the first researcher right after the navigated rTMS (real or sham).

Brunnstrom Movement Therapy

BMT is widely used by physical and occupational therapists in clinical practice. In the BMT method, motor synergies are created by benefiting from pathological reflexes, proprioceptive and cutaneal impulses, extension, and positioning. Then these are split to establish normal and functional movements (17, 18). BMT deals with the therapy of hand functions independently from the upper extremity as the recovery of hand function does not always go hand-in-hand with the recovery of the arm. Since the hand has different stages of recovery from the upper extremity, its handling and control includes specific techniques (17, 19).

Measurements

In the evaluation of the patients, demographic features in Table 1. Cognitive function was measured with the Mini-Mental State Examination (MMSE), and upper extremity and hand motor functions were measured with the Brunnstrom recovery stages (BRS). Patients were evaluated while in a sitting position on a stool.

Table 1. Patient demographic features

	Treatment group (n=10)	Control group (n=11)	p
Age, years (mean±SD)	55.70±14.92	64.54±9.38	0.158
Gender (female:male)	3:7	5:6	0.659
BMI (kg/m²)	24.72±3.54	26.73±2.34	0.159
Brain side affected by stroke R	5	6	0.397
L	5	6	0.397
Time after stroke (month)	10.45±21.80	24.50±23.88	0.890
MMSE score	28.30±2.58	28.54±1.96	1.000
rMT	45.80±5.57	41.09±1.81	0.002*

BMI: body mass index; R: right; L: left; MMSE: Mini-Mental State Examination; rMT: resting motor threshold

* p≤0.05

Table 2. The Brunnstrom Recovery Stages (BRS) (wrist, hand, upper extremity) in the treatment and control group

		Pre-treatment			Post-treatment tenth day			Post-treatment first month			Post-treatment third month			
		Mean±SD	Median (min-max)	p	Mean±SD	Median (min-max)	p	Mean±SD	Median (min-max)	p	Mean±SD	Median (min-max)	p	p within
BRS-wrist	GI	3±1.15	3 (2-5)	0.282	3.5±1.58	3.5 (2-6)	0.654	3.5±1.51	3.5 (2-6)	0.605	3.7±1.64	3 (2-6)	0.971	0.063
	G2	3.5±0.97	4 (2-5)		3.7±1.06	4 (2-5)		3.8±1.14	4 (2-5)		3.7±1.16	4 (2-5)		0.159
BRS-hand	GI	3.2±1.14	3.5 (2-5)	0.173	3.9±1.45	4 (2-6)	0.863	3.8±1.48	4 (2-6)	0.756	4.3±1.34	4.5 (2-6)	0.579	0.001*
	G2	3.9±0.99	4 (2-5)		4±0.94	4 (2-5)		4±0.94	4 (2-5)		4±0.94	4 (2-5)		0.981
BRS-upper extremity	GI	3.4±1.17	3.5 (2-5)	0.251	4.1±1.29	3.5 (3-6)	0.705	3.9±1.45	4 (2-6)	0.512	4.2±1.23	4 (3-6)	0.853	0.003*
	G2	4±0.82	4 (3-5)		4.2±0.92	4.5 (3-5)		4.3±0.95	5 (3-5)		4.3±0.95	5 (3-5)		0.066

GI: treatment group; G2: control group; SD: standard deviation; p: p between (intergroup); p within: intragroup

* p≤0.05

Mini-Mental State Examination: The MMSE is a standardized instrument for the bedside evaluation of cognitive function. It consists of a questionnaire with 11 items that assess orientation, memory (registration and recall), and attention, as well as calculation, language, and construction functions. The maximum total score on the MSSE is 30 points (20).

The patients were measured while sitting on a chair without back support.

Assessment of Brunnstrom Recovery Stages: The patients of the treatment group and the control group were classified as the stages of upper extremity, wrist, and hand motor recovery (Stages 1-6), according to the motor tests identified by Brunnstrom. The stages were identified in accordance with the motor tests at each stage. In BRS, spasticity development, existence of flexor and extensor synergies, change in synergies, movement independent from synergy, and passage to normal movement were assessed for the upper extremity (17). For the wrist, wrist stabilization for grip in elbow extension and flexion positions, wrist flexion and extension movement while clenching the hand, and circumduction were tested. Grip types and finger movements were assessed for the hand.

Proprioceptive Sense Assessment: Proprioceptive sense assessment was tested by getting the patient to perform passive motion on the affected side and repeating the motion with the unaffected side extremity or describing it (17). In our study, the sense evaluation of the patients was performed with sense tests that included shoulder, elbow, wrist, finger proprioceptive sense, and finger touch localization. For the evaluation of the wrist proprioceptive sense, the patients were in a sitting position, their arms supported with a pillow while the forearm was in pronation. A second researcher, who was doing the measurement while the patient's eyes were closed, moved the shoulder, elbow, wrist, and fingers of the disabled side towards various directions (flexion, extension). The patient was asked to reproduce the action with their sound wrist.

Finger Touch Localization Assessment: While the patient sat in the same position, the palmar surfaces of the fingers were poked one by one with a soft-tip pencil. The patient was asked to tell which finger was poked as his or her eyes remained closed. To be able to define all sense measurements numerically, points were assigned as 0, 1, or 2 for no sense, insufficient sense, and intact sense, respectively (19).

Muscle Tone Evaluation: The muscle tone (spasticity) measurement of the patients was done with the MAS as the patients were in a sitting position. The measurement was performed on the shoulder, elbow, wrist, and finger and scored as 0, 1, 1+, 2, 3, or 4 (21, 22).

All the tests used for measurement were implemented in the pre-treatment, post-treatment tenth day, post-treatment first month, and post-treatment third month stages.

This study was approved by the local ethics committee (ethical committee for human research, university hospital protocol number 2012/15-06). Informed consent was obtained from all patients before inclusion.

Statistical Analysis

The data was analyzed with Statistical Package for Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA) package program. Continuous variables were given as average ± while median and categorical variables were given is numbers (percent). For independent group comparisons, the Mann-Whitney U test and the chi-square analysis were used. The Wilcoxon rank test was also used. The Friedman test and the Cochrane Q test were used for dependent group comparisons. A $p<0.05$ was considered statistically significant.

RESULTS

Twenty-one stroke patients were involved in this study that aimed at evaluating the effect of navigated rTMS and BMT combination on upper extremity and hand functions. Evaluation of all patients in the treatment group at four separate times (pre-treatment, post-treatment tenth day, post-treatment first month, and post-treatment third month) was completed. The post-treatment third month evaluation of only one patient in the control group was unable to be completed.

Before the study, a comparison of the treatment group and the control group showed that there were no significant differences between the score averages of age, gender, body mass index (BMI), brain side affected by stroke, stroke time, and pre-treatment MMSE (Table 1). Our groups were homogeneous for demographic and clinical properties. A significant difference between the pre-treatment rMT values of two groups was found. The treatment group (45.80±5.57) was put through a higher value of rMT than the control group (41.09±1.81). Patient demographic features are described in Table 1.

Table 3. Scores of wrist proprioceptive sense and finger touch llocalization in the treatment and control group

		Insufficient-None		Intact		Total			
	Group	n	%	n	%	n	p between	p within GI	p within G2
Wrist proprioceptive sense pre-treatment	GI	5	100	5	31.3	10	0.012*		
	G2	0	0	11	68.8	11			
Wrist proprioceptive sense post-treatment tenth day	GI	4	100	6	35.3	10	0.035*	0.494	0.392
	G2	0	0	11	64.7	11			
Wrist proprioceptive sense post-treatment first month	GI	4	100	6	35.3	10	0.035*		
	G2	0	0	11	64.7	11			
Wrist proprioceptive sense post-treatment third month	GI	3	75	7	43.8	10	0.582		
	G2	1	25	9	56.3	10			
Finger touch pre-treatment	GI	7	77.8	3	25	10	0.03*		
	G2	2	22.2	9	75	11			
Finger touch post-treatment tenth day	GI	4	66.7	6	40	10	0.361	0.223	0.392
	G2	2	33.3	9	60	11			
Finger touch post-treatment first month	GI	5	83.3	5	33.3	10	0.063		
	G2	1	16.7	10	66.7	11			
Finger touch post-treatment third month	GI	5	83.3	5	35.7	10	0.141		
	G2	1	16.7	9	64.3	10			

GI: treatment group; G2: control group; p: intergroup; p within: intragroup

* p≤0.05

Table 4. Spasticity measurements of shoulder, elbow, wrist, and hand of MAS scores of the patients

		Pre-treatment			Post-treatment tenth day			Post-treatment first month			Post-treatment third month			
		Mean±SD	Median (min-max)	p	Mean±SD	Median (min-max)	p	Mean±SD	Median (min-max)	p	Mean±SD	Median (min-max)	p	p within
MAS	GI	2.9±0.57	3 (2-4)	0.55	3.1±0.57	3 (2-4)	0.22	2. 9±0.57	3 (2-4)	0.38	2.9±0.57	3 (2-4)	0.97	0.572
Shoulder	G2	2.64±0.67	3 (1-3)		2.64±0.67	3 (1-3)		2.64±0.5	3 (2-3)		2.9±0.32	3 (2-3)		0.101
MAS	GI	3±0.67	3 (2-4)	0.38	3.2±0.63	3 (2-4)	0.13	2.9±0.88	3 (1-4)	0.46	2.9±0.57	3 (2-4)	0.97	0.392
Elbow	G2	2.64±0.67	3 (1-3)		2.64±0.67	3 (1-3)		2.73±0.47	3 (2-3)		2.9±0.32	3 (2-3)		0.162
MAS	GI	2.4±0.7	2.5 (1-3)	0.34	2.6±0.84	3 (1-4)	0.70	2.5±1.08	3 (0-4)	0.75	2.6±0.84	3 (1-4)	0.43	0.585
Wrist	G2	2.73±0.79	3 (1-4)		2.73±0.79	3 (1-4)		2.73±0.47	3 (2-3)		2.9±0.32	3 (2-3)		0.532
MAS	GI	2.4±0.7	2.5 (1-3)	0.34	2.6±0.84	3 (1-4)	0.70	2.3±0.95	2.5 (0-3)	0.19	2.4±0.7	2.5 (1-3)	0.12	0.096
Hand	G2	2.73±0.79	3 (1-4)		2.73±0.79	3 (1-4)		2.82±0.4	3 (2-3)		2.9±0.32	3 (2-3)		0.532

GI: treatment group; G2: control group; SD: standard deviation; p: intergroup; p within: intragroup

Between the treatment group and control group patients, there were no significant statistical differences obtained from pre-treatment, post-treatment tenth day, post-treatment first month, and third month BRS-wrist, BRS-hand, and BRS-upper extremity (p≥0.05). Intragroup comparison of the treatment group patients showed a statistically significant difference between the BRS-hand scores in the third month before and after the treatment (p≤0.05). Intragroup comparison of the treatment group patients showed a statistically significant difference between the upper extremity scores in the third month before and after the treatment (p≤0.05) (Table 2).

Due to the rareness of the patients in the treatment group and the control group, the scores of the patients who scored 0 and I in proprioceptive sense measurement were evaluated together. Between the treatment group and control group patients, there were significant statistical differences obtained from pre-treatment, post-treatment tenth day, and first month wrist proprioceptive sense evaluations (p≤0.05). On the other hand, a significant difference was not encountered in the post-treatment third month test (p≥0.05) (Table 3). From the pre-treatment, post-treatment tenth day, post-treatment first month, and post-treatment third month evaluations of shoulder, elbow, and finger proprioceptive sense evaluations, a statistically significant difference between the treatment group patients and control group patients was not found (p≥0.05).

The only statistically significant difference between the treatment group and control group patients was found in the pre-treatment finger touch localization measurements (p≤0.05). However, there was no statistical difference in post-treatment tenth day, first month, and third month (p≥0.05) (Table 3).

Intragroup comparison of the patients of the treatment group and the control group did not reveal a statistically significant difference in terms of post-treatment tenth day, first month, and third month shoulder, elbow, finger, and wrist proprioceptive sense and finger touch localization assessments before and after treatment ($p \geq 0.05$).

There was not a statistically significant difference between the shoulder, elbow, wrist, and hand MAS scores of the treatment group and the control group in pre-treatment, post-treatment tenth day, post-treatment first month, and post-treatment third month evaluations ($p \geq 0.05$) (Table 4). The treatment group and the control group did not show any statistically significant difference in terms of MAS scores from pre-treatment, post-treatment tenth day, post-treatment first month, and post-treatment third month evaluations in their own rights ($p \geq 0.05$) (Table 4).

DISCUSSION

Though mild, an insufficiency in the upper extremity functions of stroke patients affects the quality of life negatively, and 89% of hemiparetic patients have been reported to have sensory deficits in upper extremities (23, 24). In stroke rehabilitation protocols, generally motor insufficiencies are focused on. In rehabilitation, however, sensory deficits as well as motor insufficiencies must be identified and treated (25). Stroke rehabilitation in Turkey usually focuses on independent mobilization and walking, neglecting rehabilitation and function due to the late recovery of the upper extremity (26). Our study was planned with the aim of investigating the effect of various therapy methods implemented on stroke patients on the recovery of the upper extremity. rTMS and BMT were handled as different treatment methods. For years, physiotherapists used the BMT, with which they planned the treatment in accordance with clinical decision making and assessment findings, on stroke patients very frequently. However, it can be seen that the results of BMTs performed using BRS are not adequately involved in studies. While using BRS is short, easy, and one-dimensional, its validity has been performed (27). In our study, we preferred BRS for the assessment of the patients and BMT since it focuses specifically on the treatment of the upper extremity and the hand.

Another method, the transcranial magnetic simulation (TMS), is also used by physiotherapists in international brain research laboratories for treatment purposes. The TMS is a non-invasive, pain-free, and applicable method that is used for mapping cortical motor representation in normal and pathological cases. Also, the repeated training of the TMS leads to the betterment of the motor functions of the nervous system and plasticity (28). In our study, rTMS was performed as navigated rTMS under the guidance of MRI. Our reason for using navigated rTMS was to establish the localization of our simulation in the targeted area on the brain. Each rTMS application was performed on the unaffected motor cortex hand region (the same region each time), and standardization was established.

The fundamental treatment has been reported to be the activation of the affected motor cortex and the modulation of the sensory afferents in the rehabilitation of the upper extremity in stroke patients (29, 30). Abiding by this principle, we aimed at improving upper extremity functions via inhibiting the unaffected motor cortex with I Hz rTMS.

Intragroup assessment of the patients in the treatment group (receiving real rTMS and BTM) reveals that only the BRS-hand and BRS-upper extremity stage score averages were significantly increased ($p \leq 0.05$) (Table 2). This shows that the upper extremity and the motor functions of the hand were improving. However, a statistically significant BRS difference between the control group patients receiving only BMT was not found. Therefore, it is safe to say that our rTMS implementation contributes to hand and upper extremity motor functions. The possible mechanism of rTMS's ability to improve motor functions is explained as follows: inter-hemisphere inhibition decreases in the hemisphere impulsed with low-frequency rTMS, which results in increased neural activity in the perilesional area (11, 14, 15).

It has been reported that the preservation of the sense of position after a stroke is associated with motor recovery of the upper extremity and that it is a valid prognostic finding for the prediction of the motor recovery degree in the long run (6, 7). As an adverse opinion, it has been stated that proprioceptive deficits are independent from motor deficits (8). Even if some patients can show motor recovery, it is not safe due to insufficient proprioceptive sense, and there is negative correlation between them (31).

In our study, the only statistically significant difference (in favor of the control group) in the proprioceptive sense was in the tenth day and first month before and after the treatment (Table 3). We can say that the wrist proprioceptive sense was developed via BMT in the control group subjected to sham rTMS with BMT. In any case, the BMT approach that we used included techniques like touching, tapping, stroking, etc., which contribute to proprioceptive sense improvement (17, 18). A significant difference between the groups was not found in terms of shoulder and elbow proprioceptive sense. It has been reported that post-stroke motor recovery occurs usually from the proximal area (shoulder) to the distal area (hand), yet information regarding the direction of proprioceptive recovery was not found. Semrau et al. (8) have set forth the differences between the robotic test and motor and sense recovery after stroke (17). They have stated that proprioceptive sense assessment and treatment during stroke treatment is difficult and that only one study revealed the relationship between proprioceptive function and motor recovery regarding this matter.

Our study revealed a significant difference (in favor of the control group) between the treatment group and the control group only in terms of pre-treatment finger touch localization (Table 3). However, it can be seen that the wrist proprioceptive sense and the finger touch localization of the control group has a higher intact (sense present) percentage than the treatment group in the pre-treatment period. According to our results, rTMS did not contribute to proprioceptive sense.

Etoh et al. (13) have reported that the combination of I Hz rTMS and repetitive facilitation exercises improves the upper extremity motor functions in chronic stroke patients as against rTMS,

but it does not alter spasticity. As the reason for spasticity not to change, they have specified that the suitability of the MAS is controversial, although it is widely used. Previous studies have reported that the reason for the decline in spasticity may be associated with the brain area that rTMS stimulates, duration, or frequency.

We found in our study that the MAS scores (spasticity) of both groups from the tenth day, first month, and third month before and after the treatment remained the same. We believe that more objective assessments should be used instead of valid MAS, which is widely used in clinics. We also believe that spasticity can change during the course of the stroke, that it can stem from the patient or the environment, and that the sooner spasticity gets established, the faster normal movement can be achieved.

Kakuda et al. (11) implemented unaffected hemisphere 1 Hz rTMS and occupational therapy combination on stroke patients for 15 days. At the end, they observed that the MAS scores (spasticity) decreased in elbow, wrist, and finger flexor muscles. However, they did not report any change regarding spasticity in their previous study, in which they implemented the same procedure for 6 days. However, they could not explain whether the decrease of the spasticity was due to rTMS or occupational therapy as this study did not include a control group.

Galvao et al. (32) implemented rTMS (1 Hz, 90% of the motor threshold, 1500 pulses, 10 sessions) on the motor cortex in the treatment group (10 patients) and physiotherapy (3 days/week) while they implemented sham rTMS and physiotherapy (3 days/week) in the control group (10 patients), finding that rTMS decreases spasticity in at least one month. They described the possible mechanism here as in the previous studies. The inhibitor rTMS (≤1 Hz) is primarily responsible for decreasing the unaffected hemisphere cortical excitability; it secondarily increases the affected hemisphere cortical excitability. This leads to decreased spasticity by dilating the descending corticospinal tracts. Moreover, they reported that the MAS is not very suitable for spasticity assessment, although it is frequently used in clinics and more technological, versatile methods are needed. We also did not find a significant difference between the MAS scores of both groups, so we did not detect any increase or decrease in spasticity. The reason for this can derive from the assessment of the MAS scores as well as the factors affecting spasticity (temperature, the psychology of the patient, joint reactions, the attitude of the assessor to the patient, tone of voice, etc). Galvao et al. (32) also reported that the sound that needs to be in the setting cannot be given, as in real rTMS, in the sham rTMS that they applied on their control group, although a real implementation was not performed and that they were unable to fulfill the conditions for a full sham rTMS. We believe that this can be affect on the study results. We, as we did in our study, are of the opinion that the blindness of not only the patients but also the assessor will contribute to the results in a healthier way.

The limitations and positive aspects of our work can be expressed as follows. Even though the number of patients in our study was low, they are consistent with the literature. In addition, long-term evaluations were not performed. The existence of a control group, the fact that the assessor and the patients were blind to rTMS, and that monitoring took place for up to three months, navigated rTMS use are its advantages. Also, this is the first study that investigates the effect of rTMS and BMT on proprioceptive sense in stroke patients.

Ultimately, it was concluded that the combination of rTMS and BMT for stroke patients improves the motor functions of the hand and upper extremity in treatment group cases from before the treatment to the third month after the treatment. It was observed that the rTMS-BMT combination improved only BMT wrist proprioceptive sense in treatment and control group cases from before treatment to the first month after treatment, but it had no effect on spasticity.

We believe that future studies conducted with low-frequency rTMS, and other physiotherapy rehabilitation approaches such as constraint-induced movement therapy or the Bobath approach and involving a greater number of patients, will contribute to the rehabilitation of stroke patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University School of Medicine (Protocol Number: 2012/15-06).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.Ö., V.Ö., R.Ç., B.K.; Design - M.Ö., V.Ö., R.Ç., B.K.; Supervision - M.Ö., V.Ö., R.Ç., B.K.; Resource - M.Ö., V.Ö., R.Ç., B.K.; Materials - M.Ö., V.Ö., R.Ç., B.K.; Data Collection and/or Processing - M.Ö., V.Ö., R.Ç., B.K.; Analysis and /or Interpretation - M.Ö., V.Ö., R.Ç., B.K., F.K.; Literature Search; M.Ö., V.Ö., B.K., F.K.; Writing - M.Ö., V.Ö., R.Ç., B.K., F.K.; Critical Reviews - M.Ö., B.K.,F.K.

Acknowledgements: The authors would like to thanl Prof. Süleyman Men from the Department of Radiology, Dokuz Eylül University School of Medicine for his analysis of brain MRI data and technical support and Göker Keser (PT, MSc) for his assistance with data collection.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Edin BB. Cutaneous afferents provide information about knee joint movements in humans. J Physiol 2001; 531:289-297. [CrossRef]
2. Hagert E. Proprioception of the wrist joint: a review of current concepts and possible implications on the rehabilitation of the wrist. J Hand Ther 2010; 23:2-16. [CrossRef]
3. Ribeiro F, Oliveira J. Aging effects on joint proprioception: the role of physical activity in proprioceptive sense preservation. Eur Rev Aging Phys Act 2007; 4:71-76. [CrossRef]
4. Hughes CM, Tommasino P, Budhota A, Campolo D. Upper extremity proprioception in healthy aging and stroke populations, and the effects of therapist- and robot- based rehabilitation therapies on proprioceptive function. Front Hum Neurosci 2015; 9:120. [CrossRef]

5. Tyson S, Hanley M, Chillala J, Selley AB, Tallis RC. Sensory loss in hospital-admitted people with stroke: characteristics, associated factors and relationship with function. Neurorehabil Neural Repair 2008; 22:166-172. [CrossRef]
6. Dukelow SP, Herter TM, Moore KD, et al. Quantitative assessment of limb position sense following stroke. Neurorehabil Neural Repair 2010; 24:178-187. [CrossRef]
7. Semrau JA, Herter TM, Scott SH, Dukelow SP. Robotic identification of kinesthetic deficits after stroke. Stroke 2013; 44:3414-3421. [CrossRef]
8. Semrau JA, Herter TM, Scott SH, Dukelow SP. Examining differences in patterns of sensory and motor recovery after stroke with robotics. Stroke 2015; 46:3459-3469. [CrossRef]
9. Celnik P, Hummel F, Harris-Love M, Wolk R, Cohen LG. Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. Arch Phys Med Rehabil 2007; 88:1369-1376. [CrossRef]
10. Karaduman A. Hemipleji rehabilitasyonunda nörofizyolojik yaklaşımlar ve nörogelişimsel tedavi. In: Karaduman A, Yıldırım SA, Yılmaz ÖT eds İnme sonrası fizyoterapi rehabilitasyon. 2013; 125-154.
11. Kakuda W, Abo M, Kobayashi K, et al. Low-frequency repetitive transcranial magnetic stimulation and intensive occupational treatment for poststroke patients with upper limb hemiparesis: preliminary study of a 15-day protocol. Int J Rehabil Res 2010; 33:339-345. [CrossRef]
12. Kakuda W, Abo M, Kobayashi K, et al. Anti-spastic effect of low-frequency rTMS applied with occupational treatment in poststroke patients with upper limb hemiparesis. Brain Inj 2011; 25:496-502. [CrossRef]
13. Etoh S, Noma T, Ikeda K, et al. Effects of repetitive trascranial magnetic stimulation on repetitive facilitation exercises of the hemiplegic hand in chronic stroke patients. J Rehabil Med 2013; 45:843-847. [CrossRef]
14. Takeuchi N, Tada T, Toshima M, Chuma T, Matsuo Y, Ikoma K. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. J Rehabil Med 2008; 40:298-303. [CrossRef]
15. Nowak DA, Grefkes C, Dafotakis M, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. Arch Neurol 2008; 65:741-747. [CrossRef]
16. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, 1996 June 5-7, 1996. Electroencephalogr Clin Neurophysiol 1998; 108:1-16. [CrossRef]
17. Livanelioğlu A, Kerem M. In Brunnstrom Yöntemi In (eds) Otman AS, Karaduman A, Livanelioğlu A Kerem M, Aksu S, Köse N, Aras Ö, Meriç A Hemipleji rehabilitasyonunda nörofizyolojik yaklaşımlar. 2010; 16-56.
18. Edwards S. An physioterapy approaches to the treatment of neurological conditions and historical perspectives. In: Edwards S ed Neurological physiotherapy. 1996; 3-14.
19. Sawner KA, LaVigne JM, Brunnstrom S. Brunnstrom's movement treatment in hemiplegia: a neurophysiological approach: Lippincott; 1992.
20. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc, 1992; 40:922-935. [CrossRef]
21. Li F, Wu Y, Li X. Test-retest reliability and inter-rater reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in hemiplegic patients with stroke. Eur J Phys Rehabil Med 2014; 50:9-15.
22. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987; 67:206-207. [CrossRef]
23. Carod-Artal J, Egido JA, González JL, Varela de Seijas E. Quality of life among stroke survivors evaluated I year after stroke: experience of a stroke unit. Stroke 2000; 31:2995-3000. [CrossRef]
24. Sullivan JE, Hedman LD. Sensory dysfunction following stroke: incidence, significance, examination, and intervention. Top Stroke Rehabil 2008; 15:200-17. [CrossRef]
25. Connell LA, Lincoln NB, Radford KA. Somatosensory impairment after stroke: frequency of different deficits and their recovery. Clin Rehabil 2008; 22:758-767. [CrossRef]
26. Hüseyinsioğlu BE, Özdinçler AR, Oğul EA, Krespi Y. Reliability And Validity Of Turkish Version Of Motor Activity Log-28. Turk J Neurol 2011; 17:83-89.
27. Huang CY, Lin GH, Huang YJ, et al. Improving the utility of the Brunnstrom recovery stages in patients with stroke: validation and quantification. Medicine 2016; 95:e4508.
28. Butler JA, Wolf SL. Putting the brain on the map: Use of transcranial magnetic stimulation to assess and induce cortical plasticity of upper-extremity movement. Phys Ther 2007; 87:719-736. [CrossRef]
29. Tüzün EH, Karaduman A. İnmeli hastalarda kanıta dayalı rehabilitasyon uygulamaları In: Karaduman A, Yıldırım SA, Yılmaz ÖT eds İnme sonrası fizyoterapi rehabilitasyon. 2013; 247-268
30. Oujamaa L, Relave I, Froger J, Mottet D, Pelissier JY. Rehabilitation of arm function after stroke. Literature review. Ann Phys Rehabil Med 2009; 52:269-293. [CrossRef]
31. Carey LM, Oke LE, Matyas TA. Impaired limb position sense after stroke: a quantitative test for clinical use. Arch Phys Med Rehabil 1996; 77:1271-1278. [CrossRef]
32. Barros Galvão SC, Borba Costa dos Santos R, Borba dos Santos P, Cabral MEI, Monte-Silva K. Efficacy of coupling repetitive transcranial magnetic stimulation and physical treatment to reduce upper-limb spasticity in patients with stroke: a randomized controlled trial. Arch Phys Med Rehabil 2014; 95:222-229.[CrossRef]