**RESEARCH PROTOCOL**

**Name of the Research:**

Clinical and electrophysiological evaluation of the effect of adjuvant peripheral magnetic stimulation in the treatment of post-stroke ankle flexor spasticity-randomized controlled study

**Nature of the Research**

Thesis

**Type of Research**

Prospective, double-blind randomized sham-controlled study

**Center(s) Participating in the Research:**

Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation

**Principal Researcher:** (Thesis advisor)

Name: Prof. Dr. Sehim Kutlay

Position and Title: Faculty Member of Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation

Responsibility in Research: Planning and supervision of the study, statistical analysis and interpretation of data, interpretation of results, conversion of results into scientific publications.

Signature:

**Assistant Researcher:**

Name: Prof. Dr. Haydar Gok

Position and Title: Faculty Member of Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation

Responsibility in Research: Collection of study data, statistical analysis and article writing

Signature:

**Assistant Researcher:**

Name: Dr. Secilay Gunes

Position and Title: Lecturer at Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation

Responsibility in Research: Collection of study data, statistical analysis and article writing

Signature:

**Assistant Researcher: (Thesis research assistant)**

Name: Dr. Huseyin Oguzhan Aslantas

Position and Title: Research Assistant at Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation

Responsibility in Research: Conductor of the study, Collection of study data, statistical analysis and article writing

Signature:

**Assistant Researcher:**

Name: Dr. Semra Ozkan

Position and Title: Research Assistant at Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation Research Assistant

Responsibility in Research: Collection of study data, statistical analysis and article writing

Signature:

**The Setting Where the Research will be Conducted**

Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation Neurorehabilitation Unit

**Reason and Purpose of the Study**

Cerebrovascular event (CVE) is a disease characterized by loss of strength in one half of the body, speech disorder, gait and balance disorder and slowing of mental functions due to occlusion or bleeding in the cerebral arteries. It is the second leading cause of death and the third most common cause of disability worldwide (1). After upper motor neuron damage with cerebrovascular event, descending pathways involved in motor control are destroyed and a clinic called upper motor neuron syndrome (UMNS) emerges. This syndrome consists of positive (spasticity, increased deep tendon reflexes, clonus, flexor, and extensor spasms) and negative (weakness, loss of skill, fatigue) findings. Spasticity is a common positive finding of UMNS, and it is called velocity-dependent increase in muscle tone or tonic stretch reflexes due to disruption of supra-spinal inhibitory signals (1) (2). Increases in tone in spastic muscles cause serious disability in patients by affecting the functional work of muscles in velocity-dependent voluntary activities. Studies show that 40-60% of stroke patients are affected by spasticity (3).

It is necessary to evaluate spasticity correctly in order to manage spasticity, which affects the functionality and daily living activities of the patients. There are many clinically applied evaluation methods to evaluate spasticity. The main evaluation methods are clinical evaluation scales, biomechanical evaluations, and electrophysiological measurements. The most used clinical assessment scale is the Modified Ashworth Scale (MAS). This scale scores muscle tone from 0 (normal) to 4 (severe) for spasticity. Although it is easy to use, it does not assess the velocity-dependent component of spasticity. For this reason, the Tardieu scale was developed in 1954 and the Modified Tardieu scale was developed in 1999. They are relatively more objective and allow to assess the velocity-dependent component of spasticity.

Another measurement method used to evaluate spasticity is electrophysiological reflex studies. For this purpose, the most used reflex study in EMG laboratories is the Hoffman reflex (H-reflex). This reflex is an analogue of the monosynaptic stretch reflex. H-reflex is obtained from the triceps surae muscle of the calf by stimulating the posterior tibial nerve with a low-intensity electrical stimulus from the posterior of the popliteal fossa. The conduction time of the H-reflex ranges from 26 to 34 ms. In spasticity, the H reflex latency does not change but the H/M ratio increases. Electrophysiological tests are used clinically especially to evaluate treatment responses (4) and they are frequently used tools in the examination of changes in spinal cord function and spinal reflexes in spastic patients.

The treatment of spasticity, which affects the patient's activity and participation and quality of life by causing clinical consequences such as pain, decreased range of motion (ROM) and postural disorders, is one of the important components of stroke rehabilitation. Therapeutic interventions for spasticity include surgical, pharmacological treatments as well as non-pharmacological treatments such as stretching exercises, thermotherapy, transcutaneous electrical stimulation, and biofeedback. They are used to reduce pathological muscle tone and stimulate neuroplasticity. Pharmacological treatments include antispastic drugs, neuromuscular blockade with phenol, alcohol and botulinum toxin injection and intrathecal baclofen administration. Repetitive peripheral magnetic stimulation (rPMS) is an innovative and minimally invasive treatment option that has been used in the treatment of spasticity. It is a physical therapy method based on the interaction between a high-intensity electromagnetic field and the human body. rPMS treatment involves passing an electric current through a magnetic coil placed in the applicator, creating a vertical magnetic field, and stimulating the muscle or nerve (5). In the current literature, there are studies in which rPMS is used in the treatment of spasticity caused by many different causes such as stroke, multiple sclerosis, spinal cord injury, and cerebral palsy (6) (7) (8) (9). It has been shown that repetitive contraction-relaxation cycles created by rPMS increase proprioceptive input from the affected extremity (10). rPMS cause muscle contraction by stimulating motor axons like NMES, but rPMS can penetrate the deeper layers of the muscles, is painless and has no reported side effects (5). Neurophysiological studies have revealed that rPMS tend to increase the amplitude of motor evoked potentials (9) (11) (12) and alter motor cortex excitability (13) (14). There are publications reporting that rPMS may also have an effect in cases such as gait disturbance, shoulder problems, etc. that occur after cerebrovascular disease (7) (15) (16) (17) (18). The few studies in the literature are generally studied with small sample groups and without a control group. However, to the best of our knowledge, there is no double-blind randomized sham-controlled trial investigating the efficacy of rPMS for lower extremity spasticity in stroke patients.

This study aimed to clinically and electrophysiologically investigate the effect of rPMS treatment in ankle plantar flexor spasticity after stroke.

**Material/ Method**

**Volunteer Qualification:**

Patients with post stroke ankle flexor muscle spasticity who accepted to participate to study during their neurorehabilitation treatment at Neurorehabilitation Unit will be invited if they met inclusion criteria.

**Key Inclusion Criteria:**

1) Being diagnosed with stroke according to the definition of the World Health Organization (1989)

2) Being over 18 years old

3) Having a stroke confirmed by Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

4) Patients with spasticity between 1 and 3 according to the Modified Ashworth Scale (MAS) in the lower extremity plantar flexor muscles

5) Wellness of the patient's general condition after stroke

**Key Exclusion Criteria:**

1) Patients treated with botulinum toxin, phenol, alcohol injection for spasticity in the last 6 months

2) Patients who have previously undergone antispastic surgery to the treatment area

3) Patients with a change in oral antispastic drug use in the last 6 months

4) Patients with fixed ankle contracture

5) Patients with signs of acute inflammation in the treatment area

6) Patients with bleeding diathesis

7) Patients with implanted devices (cardiac pacemaker, cochlear implant, drug pumps)

8) Patients with vascular problems such as deep vein thrombosis, phlebitis, varicose veins, arterial disease

9) Patients with a history of cancer in the treatment area

10) Pregnancy

11) Patients with metal implants in the treatment area

12) Patients with nonunion fractures at the treatment site

Patients who meet the inclusion criteria and volunteer to participate in the study will be included in the study. The study will be executed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines. Informed consent forms will be obtained from all patients.

**Intervention**

Patients included in the study will be randomized according to the Random Allocation Software (RAS) program and divided into two groups as the treatment group and the sham group. Ten sessions of stretching exercises will be applied to all patients once a day, five sessions a week, with each session lasting 20 minutes. Exercise therapy, walking and balance training, and occupational therapy to improve daily living activities will be applied to all patients within the scope of the classical physical therapy and rehabilitation (FTR) program. Patients in the treatment group will also receive total ten sessions of additional peripheral magnetic stimulation therapy for the ankle plantar flexors on the hemiplegic side once a day, five sessions a week, for two weeks, each session lasting ten minutes. Sham group will not receive rPMS treatment, the device will not be operated, the probe of the device will be positioned in the same way as treatment group for ten minutes and the previously recorded working sound of the device will be heard by the patients. Patients and evaluators will not know which group the patients are in. rPMS treatment will be applied with the “BTL-6000 Super Inductive System Elite” in our clinic. rPMS treatment parameters will be adjusted to use stimulus intensity above motor threshold which is determined individually for each patient, in the way company, that developed the device, recommended in spasticity treatment. A session of treatment time is 10 minutes.

**Evaluation:**

Socio-demographic data such as gender, age, education level, occupation, background, duration of stroke, type of lesion, presence of additional disease, drugs used for spasticity, if any, botulinum toxin injection history of the volunteers included in the study will be questioned and the information will be recorded in the volunteer follow-up form. Within the scope of the study, the patients will be evaluated four times in total, before the treatment, at the end of the first session, at the end of the treatment (week 2) and two weeks after the end of the treatment. In these evaluations, MAS and modified Tardieu scale will be used in the clinical evaluation of spasticity, H latencies and H/M responses will be measured in the electrophysiological evaluation. In order to evaluate the effects of spasticity on daily life, the Barthel Index will be used, and the 6-meter walking test will be used to evaluate the walking times of the patients. In the evaluation to be made immediately after the first session, only electrophysiological measurements will be made, all parameters will be re-evaluated at the time of other evaluation times. Appointment of patients to treatment groups will be made by Dilek Kara, Head Nurse of AUTF Physical Medicine and Rehabilitation Cebeci Clinic. The study design was designed as double-blind. The treatment applications will be done by Dr. Sehim Kutlay and Dr. Semra Ozkan, and the evaluations by Dr. Huseyin Oguzhan Aslantas and Dr. Secilay Gunes, who will be blinded to the treatment groups. Statistical analysis will be done by Dr. Haydar Gok.

Outcome Measures:

1. Modified Ashworth Scale (MAS)
2. Modified Tardieu Scale
3. Evaluation of H/M responses with EMG
4. Barthel Activities of Daily Living Index (Mobility and Stairs sections)
5. 6 meters walking time

**Modified Ashworth Scale:**

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| 0 No increase in muscle tone  1 Slight increase in muscle tone, manifested by a catch and release or by minimal  resistance at the end of the range of motion when the affected part(s) is moved in  flexion or extension  1+ Slight increase in muscle tone, manifested by a catch, followed by minimal  resistance throughout the remainder (less than half) of the ROM  2 More marked increase in muscle tone through most of the ROM, but  affected part(s) easily moved  3 Considerable increase in muscle tone, passive movement difficult  4 Affected part(s) rigid in flexion or extension |

**Modified Tardieu Scale:**

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| Velocity of stretch:  V1: As slow as possible (minimizing stretch reflex)  V2: Speed of the limb segment falling under gravity  V3: As fast as possible (faster than the rate of the natural drop of the limb segment under gravity)  The quality of muscle reaction:  0- No resistance throughout the course of the passive movement  1- Slight resistance throughout the course of the passive movement, with no clear catch at precise angle  2- Clear catch at precise angle, interrupting the passive movement, followed by release  3- Fatigable clonus (<10 seconds when maintaining pressure) occurring at precise angle  4- Infatigable clonus (>10 seconds when maintaining pressure) occurring at precise angle |

**Barthel activities of daily living index:** This index evaluates physical independence in activities of daily living. It is a detailed, objective, easy-to-apply, understandable scale that evaluates all specific steps of daily living activities. A score of 0 to 20 points indicates complete dependence, 21 to 61 points severe dependence, 62 to 90 points moderate dependence, 91 to 99 points mild dependence, and 100 points complete independence.

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| **1- Feeding (10)** | 10 = independent |
| 5 = needs help cutting, spreading butter, etc., or requires modified diet |
| 0 = unable |
| **2- Transfers (bed to chair and back) (15)** | 15 = independent |
| 10 = minor help (verbal or physical) |
| 5 = major help (one or two people, physical), can sit |
| 0 = unable, no sitting balance |
| **3- Grooming (5)** | 5 = independent face/hair/teeth/shaving (implements provided) |
| 0 = needs to help with personal care |
| **4- Toilet Use (10)** | 10 = independent (on and off, dressing, wiping) |
| 5 = needs some help, but can do something alone |
| 0 = dependent |
| **5-** **Bathing (5)** | 5 = independent (or in shower) |
| 0 = dependent |
| **6-Mobility (on level surfaces) (15)** | 15 = independent (but may use any aid; for example, stick) > 45 meters |
| 10 = walks with help of one person (verbal or physical) > 45 meters |
| 5 = wheelchair independent, including corners, > 45 meters |
| 0 = immobile or < 45 meters |
| **7- Stairs (10)** | 10 = independent |
| 5 = needs help (verbal, physical, carrying aid) |
| 0 = unable |
| **8- Dressing (10)** | 10 = independent (including buttons, zips, laces, etc.) |
| 5 = needs help but can do about half unaided |
| 0 = dependent |
| **9- Bowels (10)** | 10 = continent |
| 5 = occasional accident |
| 0 = incontinent (or needs to be given enemas) |
| **10- Bladder (10)** | 10 = continent |
| 5 = occasional accident |
| 0 = incontinent, or catheterized and unable to manage alone |

**6-meter walking time:** It is measured in seconds how long it takes the patient to walk the 6 meter distance on a flat surface at his/her own pace.

**Measurement of H/M responses with EMG**

In this electrophysiological evaluation, H and M responses will be recorded as a result of stimulation with low-intensity electrical stimulus from the posterior of the popliteal fossa from the affected side while the patients are lying in the prone position (from triceps surae muscle of the calf). Measurements will be made with a KeypointTM brand device.

**Statistical analysis:**

**Number of volunteers:** In the study, when the Modified Ashworth Scale (MAS) was taken as the primary outcome variable and stage 4 patients according to MAS were not included, one unit decrease in MAS was considered significant, and a total of 68 volunteers were planned to be recruited when power analysis was performed with 80% power and 5% margin of error. However, due to the nature of the study, it was planned to include a total of 80 volunteers, with a 15% loss expected.

**\*\* Research budget:**

This study will be funded by Ankara University Scientific Research Projects (BAP) Coordination Unit.

**\*\*** **Projected Working Time**

Start date: 01.12.2021

End date: 01.06.2023

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28.09.21