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ORIGINAL ARTICLE

Priming constraint-induced movement therapy with intermittent theta burst stimulation to enhance upper extremity recovery in patients with stroke: protocol for a randomized controlled study

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Abstract

Background The treatments based on motor control and motor learning principles have gained popularity in the last 20 years, as well as non-invasive brain stimulations that enhance neuroplastic changes after stroke. However, the effect of intermittent theta burst stimulation (iTBS) in addition to evidence-based, intensive neurorehabilitation approaches such as modified constraint-induced movement therapy (mCIMT) is yet to be investigated.

Aim We aim to establish a protocol for a randomized controlled study investigating the efficiency of mCIMT primed with iTBS after stroke.

Methods In this randomized controlled, single-blind study, patients with stroke ($N=17$) will be divided into 3 groups: (a) mCIMT + real iTBS, (b) mCIMT + sham iTBS, and (c) mCIMT alone. 600-pulse iTBS will be delivered to the primary motor cortex on the ipsilesional hemisphere, and then, patients will receive mCIMT for 1 h/session, 3 sessions/week for 5 weeks. Upper extremity recovery will be assessed with Fugl-Meyer Test-Upper Extremity and Wolf Motor Function Test. Electrophysiological assessments, such as Motor-Evoked Potentials, Resting Motor Threshold, Short-Intracortical Inhibition, and Intracortical Facilitation, will also be included.

Conclusions In this study, a protocol of an ongoing intervention study investigating the effectiveness of iTBS on ipsilesional M1 prior to the mCIMT in patients with stroke is proposed. This will be the first study to research priming mCIMT with iTBS and it may have the potential to reveal the true effect of the iTBS when it is added to the high-quality neurorehabilitation approaches.

Trial registration Trial registration number: NCT05308667

Keywords Cerebrovascular accident · Neurological rehabilitation · Transcranial magnetic stimulation · Upper extremity

Introduction

Stroke is a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a cause no other than vascular causes, including cerebral infarction, intracerebral, and subarachnoid hemorrhage [1]. According to the World Stroke Organization, 12.2 million new people experience a stroke each year and unfortunately, six and a half million of these people expire due to the incident. [2]. Besides mortality, stroke is one of the major causes of morbidity around the world. Upper limb impairments in particular are reported in 48% of stroke survivors at the onset of the incident [2]. These impairments are paresis, abnormal muscle tone, decreased somatosensation, and coordination [3].

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Today, many treatment approaches based on motor control and motor learning principles are applied in treating upper extremities following a stroke. Task-specific activities, goal-oriented therapy, neurophysiological approaches, or constraint-induced movement therapy (CIMT or CI Therapy) are the most commonly used approaches that led to improved motor recovery [4]. In particular, CIMT is recommended by various current stroke management guidelines and reported to have A level of evidence for functional recovery of the upper extremity [4, 5].

It is a treatment in which a series of therapeutic approaches are applied to increase the use of the affected limb in addition to the restriction of the unaffected limb most of the day for 2 or 3 weeks [6]. Previous studies have shown that CIMT causes significant neuroplastic changes in the structure and functions of the CNS [7]. The protocol of CIMT, which includes intensive use of the affected upper extremity (6 h per day), is one of its distinguishing features and its effectiveness has been demonstrated by many studies [8, 9].

However, studies have also pointed out that patient compliance is low and fatigue is high because of this long and intensive protocol [10, 11]. In addition, the failure to provide the necessary time, and financial and human resources prevented the widespread use of CIMT in clinical practice.[11]. In view of all these deficiencies and limitations of the CIMT, modified CIMT protocols (mCIMT), which are applied with relatively less intensity, have been proposed. However, mCIMT protocols were applied in wide ranges from 45 min to 5 h a day, from 3 to 5 sessions a week for 2–10 weeks [9]. Due to the lack of consensus on the duration of mCIMT protocols, various adjunct rehabilitation methods have been added to mCIMT to decrease workload of the clinicians and healthcare expenses.

Another hot topic of the century for the recovery of upper extremity after stroke is non-invasive brain stimulation techniques. Repetitive transcranial magnetic stimulation (rTMS) has been reported to be a reliable approach to increase neuroplasticity in stroke survivors [3]. It has been found that rTMS can optimize the neuroplastic changes induced by motor training and, thus, increase the long-term effectiveness of exercise training [12].

Theta burst stimulation, which is a form of rTMS, produces currents consisting of bursts of certain intensity are applied intermittently or continuously. Intermittent theta burst stimulation (iTBS) excites the cortex and it is applied on the ipsilesional cortex, while continuous current (cTBS) produces inhibition and it is applied on the contralateral cortex. In recent studies, it has been reported that iTBS is more effective than cTBS on upper extremity recovery in stroke survivors [13]. It has also been reported that iTBS enhances recovery when applied in addition to rehabilitation in all stages of stroke (acute, subacute, or chronic) [14–16]. The biggest advantage of TBS is that the total application time is about 3 min. It provides great convenience for the patients and clinicians and, therefore, increases compliance with the treatment [17].

As mentioned above, iTBS has been a promising adjunct to the standard rehabilitation techniques. However, the effect of iTBS when added to the intensive neurorehabilitation approaches such as mCIMT is yet to be investigated. Therefore, the aim of this study is to establish a protocol for a study investigating the efficiency of mCIMT when it is primed with iTBS in patients with stroke. Our hypothesis is that applying mCIMT with iTBS would result in more enhanced motor recovery compared to the sham iTBS with mCIMT and mCIMT application alone.

Materials and methods

Study design

This study is planned as a single-blinded, placebo-controlled randomized study. The study was approved by Marmara University University Faculty of Medicine Clinical Trials Ethics Committee (date 01.06.2022—no.09.2022.614) and it will be administered according to the Ethical Principles for Medical Research Involving Human Subjects by the Helsinki Declaration. The participants will give written and verbal informed consent before the study. The study was registered in ClinicalTrials.gov (NCT05308667).

Patient selection, randomization, and blinding

The inclusion criteria for the patients are: (a) ≥ 18 years old, b) having first time, unilateral stroke in the last 12 months, c) scoring ≥ 24 points in Mini-Mental State Examination, d) being able to stand for 2 min without any help using the upper extremity as a support tool when necessary, e) having at least 10 degrees of active wrist extension starting from the angle of full flexion, and 10 degrees of extension of the MCP and IP joints of at least 2 fingers [18]. Patients who score above 2.5 points on the Motor Activity Log-28 [18], who have severe pain in the upper extremity (5 and above according to the Visual Analogue Scale) and spasticity (3 and above on the Modified Ashworth Scale), who have inadequate communication skills, visual problems or any problems which can interfere with the evaluation or therapy will not be included in the study. The exclusion criteria specific to the iTBS application were as follows: a) having conductive, ferromagnetic, or other magnetic-sensitive metals or devices implanted in the head and neck, b) history of epilepsy, and c) having cardiac stents, pace-makers, or wearable cardioverter defibrillators [19].

Three parallel groups will be employed: (a) Group 1: real iTBS + mCIMT, (b) Group 2: sham iTBS + mCIMT, and (c) Group 3: mCIMT alone. The socio-demographic and clinical data as well as baseline assessments will be performed before the randomization of the patients. The randomization will be conducted according to the order of application (i.e., 1:1:1 ratio). Participants will be assigned to the three groups one-by-one, meaning that the first participant to apply will be in Group 1, whereas the second participant will be in Group 2.

There will be two different forms of informed consent for patients in the mCIMT group and for the patients in the both iTBS application groups. Thus, patients will be blinded to their group allocation. The evaluations and the interventions will be performed by a physiotherapist with 8 years of experience.

Assessments

Eligible patients will be evaluated at the baseline and after the end of study. Each evaluation session will be performed on a separate session a day before and after the intervention. Medical history and information regarding the stroke will be retrieved from the hospital database. Sociodemographic data such as age, gender, handedness, education, etc. will be collected from the patients' and their caregivers'. Duration of the evaluation sessions will be around 1–1.5 h. The evaluations will be completed by taking into account the fatigue levels of the participants and giving rest intervals.

a. Clinical assessments

a. *Fugl-Meyer assessment*: The upper extremity part of the Fugl-Meyer Assessment (FMA-UE) will be included [20]. FMA-UE evaluates the motor (upper extremity, wrist, hand, and speed/coordination), sensory, passive range of motion, and pain levels [21, 22]. Each subheading is scored separately, and a patient can get a maximum of 66 points from the motor function section, 12 points from the sensory evaluation, and 24 points from passive range of motion and pain assessment section [21, 22]. Higher scores indicate lesser impairment levels [23]. The reliability and validity of FMA-UE is well established in stroke patients (ICC ranges between 0.971 and 0.989) [21, 24]. Excellent intra-rater and inter-rater reliability have been also demonstrated [21]. Finally, responsiveness of FMA-UE was reported to be large, since the standardized response mean (SRM) was 1.42 (95% CI 1.19–1.80) [25].

b. *Wolf Motor Function Test* (*WFMT*): The modified, 17-item version of WFMT by Morris et al. will be included [26]. The test evaluates 15 items on a time and "Functional Ability Scale (FAS)" which is a 6-point ordinal scale. Performance time and ability is determined by taking the median of these items. The remaining 2 items measure the strength of the patients [26]. The psychometric properties of WFMT have been previously reported to be satisfactory [26]. Test–retest reliability of the WFMT was 0.95 and 0.90 for FAS and performance time, respectively [26]. Inter-rater reliability was also well established (ICC for FAS ≥ 0.88 and ICC for performance time ≥ 0.90) [26].

c. *Motor Activity Log-28* (*MAL-28*): MAL-28 was developed in 2006 by Uswatte et al. [27] to evaluate the frequency (Amount Scale-AS) and quality of movement (How Well Scale-HWS) of the affected upper limb in daily life. Patients answer each question evaluating 28 daily life activities using both scales from zero (not used) to five (same as pre-stroke for AS and normal for HWS) [27, 28]. Both scales are calculated separately by taking the mean of the total item scores, and a high score indicates a high frequency and quality of movement [27, 28]. Internal consistency of the MAL-28 was reported to be high, since the Cronbach's alpha was 0.94 [27]. Both the convergent and divergent validity of the MAL-28 were established and it was found reliable (ICC for AS: 0.79 and ICC for HWS: 0.82) [27].

a Electrophysiological assessments

Participants will be evaluated by sitting in a comfortable position in a quiet room. Dantec Keypoint 3-Channel Amplifier Electromyography (EMG) device and Mag Venture-Mag Pro TMS devices will be used for the electrophysiological measurements. A circular coil will be used for cortical stimulations. Simultaneous EMG evaluation will performed with 2 cm-diameter Ag–AgCl surface electrodes placed on the impaired adductor digiti minimi (ADM) muscle. Electrodes will be placed on the body and tendon of the ADM muscle. EMG recordings will be performed with Dantec Keypoint 3-Channel Amplifier EMG device with 10 ms sweep speed and 50 µ-1 mV sensitivity, frequency filters in the range of 2 Hz-10 kHz (kilo-hertz). The evaluations will start with finding hot spot for ADM muscle on the primary motor cortex (M1) following the protocol reported on previously conducted studies [29, 30].

a. *Resting Motor Threshold* (*RMT*) *and Motor-Evoked Potentials* (*MEPs*): The RMT is defined as the "stimulus intensity that causes a minimal motor response in the target muscle via the stimulation of its hotspot on the M1" [31]. MEPs are, on the other hand, defined as "the electrical signals recorded from the descending motor pathways or from muscles following stimulation of motor pathways via non-invasive brain stimulations" [32]. In this study, for the measurement of RMT, the ADM muscle will be in completely rest and stimulation will start with 35% of the maximum stimulator output

(MSO). The MSO value will be increased by 5% until the RMT is reached [33]. The lowest stimulus intensity that could produce a MEP of 50 µV and above in at least 5 of 10 trials will be recorded as RMT [34]. 120% of the RMT will be used to determine the MEPs and the average of the amplitude ratios will be recorded as the MEPs value [35].

b. *Cortical excitability measurements*: Cortical excitability measurements of the brain are measured with paired-pulse stimulation. Paired-pulse stimulation involves a conditioning stimulus followed by a test stimulus and depending on the amplitude of these stimuli, an inhibition or facilitation occur [34]. Short intracortical inhibition (SICI) is described as "the amplitude reduction of MEPs by a subthreshold conditioning stimulus in paired-pulse stimulation techniques" [36]. Intracortical facilitation (ICF) also occur as a result of a subthreshold conditioning and suprathreshold test stimuli at an interstimulus interval (ISI) of 6–30 ms [37]. In this study, ISI will be set to 3 ms for SICI and 12 ms for ICF [30].

Interventions

a. *Group 1 (real iTBS + mCIMT)*: Patients who will be allocated in the Group 1 will be treated with the combination of real iTBS and mCIMT. This group will receive treatment for 3 sessions each week, for 5 weeks (15 sessions in total). Each session will last around 1 h. mCIMT protocol will include all three aspects of CIMT, namely use of mitt, repetitive training, and transfer to activities of daily living. iTBS consisting of 600-pulse (50 Hz frequency, 200 ms intervals) will be applied before the mCIMT training and it will last around 190 s [38]. Stimulation intensity will be 80% of the RMT and it will be applied on the hot point. As contrast to the original protocol of iTBS, application will be performed on intermittent days as tested efficient in our previous work [39].

b. *Group 2* (*sham iTBS + mCIMT*): Group 2 participants will receive a sham iTBS treatment prior to therapy. Sham application will be delivered by flipping over the coil, since the output of the flipped side is much lower [16] and positioning the coil without touching the scalp, so that no current is produced in the brain. Also, sham stimulation intensity will be set at the %30 of the MSO, to create a sound similar to the real iTBS. This group received the same mCIMT as other groups (i.e., 1 h per session, 3 sessions a week for 5 weeks)

c. *Group 3* (*mCIMT alone*): As defined above, mCIMT group will also have same aspects of CIMT, namely use of mitt, repetitive training and transfer to activities of daily living and their sub-components. Task activities will be selected among the activities that the patients want to do but cannot do. If the patient does not indicate any activity, activities from MAL-28 will be incorporated.

Figure 1 shows the protocol and flow of the study.

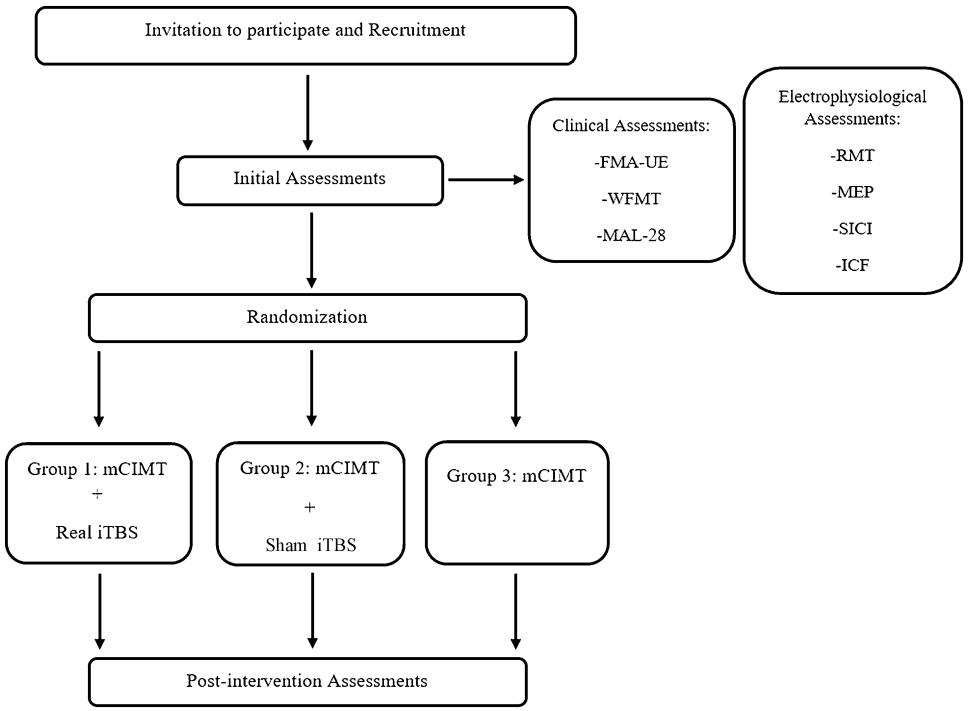

Fig. 1 Study protocol

Statistical analysis

Sample size analysis for this research is calculated in PS Power and Sample Size Calculations Version 3.0. Since the primary outcome measure of this study is FMA-UE, the calculation has been performed with the minimal clinically important difference (MCID) and standard deviations (SD) values of FMA-UE from the work of Hiragami et al. [40]. The MCID value of FMA-UE was 12.4 points and the SD value was 5.0 points in patients who had a stroke in the last month [40]. Therefore, sample size for each group is calculated as $n=5$ with 95% power and 5% type 1 error. Considering the 10% drop-out rate, the total sample size is calculated as $n=17$. Even though this estimated sample size appears small, it definitely fits to the exploratory nature of this study.

Discussion

Here, we have described the protocol of our ongoing intervention study investigating the effectiveness of iTBS on ipsilesional M1 prior to the mCIMT. This will be the first study to research priming mCIMT with iTBS.

In a recent systematic review and meta-analysis of randomized and non-randomized controlled studies [41], it was found that iTBS was efficient for increasing neuroplasticity, motor function, and use of impaired upper extremity in daily activities compared to control conditions when it was applied in addition to the rehabilitation protocols. However, the rehabilitation programs consisted of routine rehabilitation approaches and some studies did not even have training for upper extremity; instead, they include modalities such as electro-acupuncture. The control conditions were either sham iTBS or routine rehabilitation techniques alone. Authors concluded the study with recommendations for further investigation of the topic with high-quality randomized clinical trials.

In this study, we have proposed a protocol for a study with low risk of bias, since this study is planned as randomized and includes two control groups, clearly indicates the patient selection criteria, conceals the group allocation, includes blinding, and aims to minimalize missing data (ideally no missing data) [42, 43]. Additionally with today's knowledge from the literature, we know that the routine rehabilitation approaches, which does not include tailored, repetitive, intensive task training, is not adequate for helping patients with stroke to reach their full capacity. Thus, it was proposed that CIMT approaches were superior to standard rehabilitation approaches in improving upper extremity recovery [41]. Similarly, 6th edition of the Canadian Stroke Best Practice Recommendations reported that CIMT and mCIMT approaches reached Evidence Level-A (in early periods) for increasing upper extremity function [44]. Therefore, this study has a potential for revealing the true effectiveness of iTBS when it is coupled with high-quality care in patients with stroke.

Another missing points in some of the studies included in the aforementioned meta-analysis [41] is the application of 1200 pulses of iTBS. In another recent meta-analysis [45], 600-pulse iTBS showed superiority in enhancing upper limb function after stroke compared to sham conditions, whereas 1200-pulse iTBS displayed no effectiveness at all. Thus, we believe that proposing a study protocol with 600-pulse iTBS application prior to mCIMT protocol holds a relevant and highest quality of evidence in light of the current literature knowledge.

Overall, the strengths of this study are 1) randomized study design with 2 control groups and low risk of bias, 2) application of modalities with high-quality evidence and which are suggested by the recent literature findings, and 3) use of a non-invasive brain stimulation method that is quick, easy, safe, and holds a potential to increase patients' adherence. The major strength of this study is that this is the first study ever to investigate effectiveness of iTBS priming on the efficiency of mCIMT in upper extremity recovery.

However, this protocol has some limitations as well. First, the single-center nature of this study may limit the generalizability of our results to the stroke population. Second, estimated sample size may be lower; however, earlier studies reported that studies involving 15 patients may generate reliable results [46] and including repeated measures may further increase the power of the study [47]. Also, studies conducted on brain stimulation generally use smaller sample sizes compared to rehabilitation studies, since contraindications of non-invasive brain stimulation are constraining [47, 48]. Finally, as the interventions and measurements can only take place in a clinical setting, the number of enrollments to this study may be limited.

Author contributions Conceptualization: ENK, BEH, ZÖ, ZB, and AS; methodology: ENK, BEH, ZÖ, ZB, and AS; writing—original draft preparation: ENK, BEH, ZÖ, and ZB; writing—review and editing: BH, ZB, ZÖ, and AS; supervision: BEH, ZB, and AS.

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Data availability There are no linked data sets for this paper. The data are confidential, since the participant of this study were informed upon admission to the hospital that the data would remain confidential and would not be shared with third parties.

Code availability Not applicable.

Declarations

Conflict of interest None.

Ethical approval The study was approved by Marmara University Faculty of Medicine Clinical Trials Ethics Committee (date 01.06.2022—no.09.2022.614) and administered according to the Ethical Principles for Medical Research Involving Human Subjects by the Helsinki Declaration.

Consent to participate Both written and verbal consent will be obtained from the participants before the study.

Consent for publication It will be obtained from the participants.

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