Effectiveness of Intermittent Theta Burst Stimulation to Enhance Upper Extremity Recovery after Stroke: A Randomized Controlled Study

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Highlights

- Intermittent theta-burst stimulation can be applied every other day and still produce additional benefits to the modified constraint-induced movement therapy after stroke.
- Intermittent theta-burst stimulation, in addition to the modified constraint-induced movement therapy, increased the speed and strength of the impaired UE in patients with stroke.
- Even though the effect of intermittent theta-burst stimulation on decreasing disabilities in self-care was statistically insignificant, there was a clinically meaningful decrease in the disability score after the study.
- The application of intermittent theta-burst stimulation could be extended to 15 sessions instead of 10 sessions in patients with stroke without any reverse effects.

Running Title: iTBS and mCIMT in stroke

Effectiveness of Intermittent Theta Burst Stimulation to Enhance Upper Extremity Recovery after Stroke: A Randomized Controlled Study

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Declarations

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Effectiveness of Intermittent Theta Burst Stimulation to Enhance Upper Extremity Recovery after Stroke: A Pilot Study

Abstract

Objective: To first investigate the effectiveness of modified Constraint-Induced Movement Therapy (mCIMT) in low-functioning patients with stroke (PwS). Second, we aimed to investigate the efficiency of intermittent theta-burst stimulation (iTBS), applied on intermittent days, in addition to the mCIMT in PwS.

Design: Randomized, sham-controlled, single-blinded study.

Setting: Outpatient clinic.

Participants: Fifteen PwS (age 66.3 ± 9.2 years (mean ± SD); 53% female) who were in the first 1-12 months after the incident were included in the study.

Interventions: PwS were divided into 3 groups: 1) mCIMT alone, 2) mCIMT + sham iTBS, and 3) mCIMT + iTBS. Each group received fifteen sessions of mCIMT (1 hour/session, 3 sessions/week). iTBS was applied with 600-pulses on impaired M1 prior to mCIMT.

Main Outcome Measures: Upper extremity (UE) impairment was assessed with the Fugl-Meyer Test (FMT-UE), while the motor function was evaluated with the Wolf-Motor Function Test (WMFT). Motor Activity Log-28 (MAL-28) was used to evaluate the amount of use (AUS) and how well (HWS) the impaired UE movements.

Results: With-in-group analysis revealed that all groups had statistically significant improvements based on the FMT-UE and MAL-28 ($p<0.05$). However, the performance time and arm strength variables of WMFT were only increased in the mCIMT + iTBS group ($p<0.05$). The only between-group difference was observed in the intracortical facilitation in favor of the mCIMT + iTBS group ($p<0.05$). The effect size of iTBS was $f=0.18$.

Conclusion: Our findings suggest that mCIMT with and without the application of iTBS has increased the UE motor function in low-functioning PwS. iTBS applied on intermittent days may have additional benefits as an adjunct therapy for facilitating cortical excitability, increasing the speed and strength of the impaired UE as well as decreasing disability.

Keywords: Stroke, neurological rehabilitation, transcranial magnetic stimulation, motor-evoked potentials.

Clinical Trial Registration: NCT05308667

Abbreviation List: iTBS: Intermittent Theta-Burst Stimulation. mCIMT: Modified Constraint-Induced Movement Therapy. PwS: Patients with Stroke. UE: Upper extremity. FMT-UE: Fugl-Meyer Test- Upper Extremity. WMFT: Wolf-Motor Function Test. MAL-28: Motor Activity Log-28. AUS: Amount of Use Scale. HWS: How Well Scale. NIBS: Non-invasive Brain Stimulation Techniques. rTMS: Repetitive Transcranial Magnetic Stimulation. MCID: Minimal Clinically Important Difference. FAS: Functional Ability Scale. EMG: Electromyography. ADM: Adductor Digiti Minimi. M1: Primary Motor Cortex. RMT: Resting Motor Threshold. MEPs: Motor-Evoked Potentials. SICI: Short Intracortical Inhibition. ICF: Intracortical Facilitation (ICF). ISI: Interstimulation Intervals. MSO: Maximum Stimulator Output. FIM: Functional Independence Measure.

INTRODUCTION

Constraint-induced movement therapy (CIMT) is one of the most recommended approaches for upper extremity (UE) after stroke since it was reported as having Level A evidence[1–4]. It consists of three major components: i)the use of a restrictive mitt, ii)repetitive training with shaping and task activities, and iii)transfer package[5]. The protocol was created for 6 hours/day, 5 days/week for 2 or 3 weeks[4,6]. Later on, studies have shown that CIMT may cause fatigue in patients with stroke (PwS) and diminish patient compliance

to rehabilitation[7,8]. Therefore, modified CIMT protocols (mCIMT), which are less intensive, have been proposed. Even though the mCIMT protocol was also found to be successful in improving outcomes in participants with higher-functioning levels, its effectiveness in participants with lower function was not clear [9]. It has been suggested that mCIMT protocols supported with non-invasive brain stimulation techniques (NIBS) may create even larger neuroplastic effects, specifically in participants with lower function [10].

Intermittent theta burst stimulation (iTBS), an excitatory form of repetitive transcranial magnetic stimulation (rTMS), appears to enhance response to rehabilitation in PwS[11]. Additionally, having only 3 minutes of application duration gained the attention of researchers and rehabilitation professionals. iTBS provides great convenience for both the participants and clinicians and therefore, increases compliance with the treatment[12]. We hypothesized that iTBS might resolve the time-consuming nature of the mCIMT.

Therefore, this study aimed to first investigate the effectiveness of mCIMT in low-functioning PwS. Second, we aimed to investigate the efficiency of iTBS, applied on intermittent days, on UE motor recovery and cortical excitability in addition to the mCIMT in PwS. We believe the findings of this study might have proper implications for the use of both mCIMT and iTBS as an adjunct to the mCIMT in low-functioning PwS in neurorehabilitation settings.

METHODS

This was a single-blinded, sham-controlled randomized study. The study was approved by a local ethics committee (date 01.06.2022 - no. 09.2022.614). A written and verbal informed consent was collected before the study. The informed consent forms were prepared separately for mCIMT only group and iTBS-added groups. Therefore, participants were blinded to their group allocation. During the process of obtaining informed consent, all participants received comprehensive information regarding potential adverse effects. They

were instructed to promptly notify researchers in the event of experiencing any such effects. The study was registered in ClinicalTrials.gov (NCT05308667).

Participant Selection and Randomization

The participants were acquired from neurology clinics of a local hospital. The inclusion criteria for the participants were: a) ≥18 years old, b) having first a unilateral stroke in the last 12 months, c) scoring ≥24 points in the Mini-Mental State Examination, d) being able to stand for 2 minutes without any help, by using the UE as a support tool when necessary, e) being a low-functioning PwS criteria according to the Alabama University protocol[13]. Exclusion criteria were as follows: a) scoring above 2.5 points on the Motor Activity Log-28[13], b) having severe pain in the UE (≥5 points on the Visual Analogue Scale) and severe spasticity (≥3 on the Modified Ashworth Scale), c) having aphasia and/or inadequate communication skills, visual problems or any problems which can interfere with the evaluation or with therapy. The exclusion criteria specific to the TMS application were as follows: a) conductive, ferromagnetic, or other magnetic-sensitive metals or devices implanted in the head and neck, b) history of seizures, c) cardiac stents, pace-makers or wearable cardioverter defibrillators[14].

This study involved three groups: i)mCIMT alone, ii)mCIMT+sham iTBS, and iii)mCIMT+real iTBS. The randomization into the groups was conducted according to the order of recruitment (Allocation ratio 1:1:1).

Outcome Measurements

All outcome measures were assessed at the baseline (T1) and after the intervention (T3). An additional assessment at the beginning of the 11th session (T_2 assessments) was also

performed only with the Fugl-Meyer Test (FMT-UE), Wolf Motor Function Test, and electrophysiological measurements.

a. Primary Outcome Measures

- Fugl-Meyer Test- Upper Extremity (FMT-UE): FMT-UE was included in the current study to assess the motor, sensory, passive range of motion, and pain levels after stroke[15–17]. The minimal clinically important difference (MCID) for FMT-UE was reported to be 12.40 in PwS with moderate to severe hemiparesis[18].

- Electrophysiological measurements: Cortical magnetic stimulations were delivered using a Mag Venture – Mag Pro TMS device with a circular coil. Dantec Keypoint 3-Channel Amplifier Electromyography (EMG) device was used for electrophysiologic recordings (10 ms sweep speed and 50 μV sensitivity, filtered in the range of 2 Hz-10 KHz) and simultaneous EMG evaluation was performed with 2 cm diameter Ag-AgCl surface electrodes placed on the adductor digiti minimi (ADM) muscle of the impaired hand. Electrodes were placed on the body and tendon of the ADM muscle. The evaluation sessions started with finding a motor hot spot for ADM muscle on the impaired primary motor cortex (M1) following the previously reported protocol[19,20].

- **Resting Motor Threshold (RMT) and Motor-Evoked Potentials (MEPs):** The RMT was measured when the ADM muscle was at rest and stimulations started with 35% of the maximum stimulator output (MSO). The MSO value was increased by 5% until the RMT was reached[21]. The lowest stimulus intensity that could produce an MEP of 50 μV and above in at least 5 of 10 trials was recorded as RMT[22]. 120% of the RMT was used to determine the MEPs and the average of the amplitude ratios was recorded as the MEPs value[23].

- **Cortical Excitability Measurements:** Dual stimulation technique in a previously defined protocol[22] was followed to measure short intracortical inhibition (SICI) and intracortical facilitation (ICF). Interstimulation intervals (ISI) were set to 3 ms for SICI and 12 ms for ICF[20].

b. Secondary Outcome Measures

- Wolf Motor Function Test (WFMT): This study employed the modified, 17-item version of WFMT by Morris et al.[24]. The test evaluates 15 items in terms of time (i.e. performance time) and ability (i.e. Functional Ability Scale-FAS). FAS is a 6-point ordinal scale in which higher scores indicate better performance. The remaining 2 items in WFMT measure the strength of the upper limb[24].

- Motor Activity Log-28 (MAL-28): MAL-28 was developed to evaluate the frequency (Amount of Use Scale-AUS) and quality of movement (How Well Scale-HWS) of the affected upper limb during 28 daily life activities[25]. Both scales have scores from zero (not used) to five (same as pre-stroke)[25,26]**,** namely, a high score indicates a high frequency and quality of movement[25,26].

-Functional Independence Measure (FIM): FIM is a scale developed to evaluate the degree of disability and evaluates self-care, sphincter control, transfers, locomotion, communication, and social cognition. Scoring is done on a 7-point Likert scale and the higher scores indicate more independence[27]. This study only included the self-care part of the scale. The MCID value of FIM was 11 points according to a recent study[28].

Study Intervention Protocols

This study adopted the CIMT protocol developed by Taub and Uswatte [5]. CIMT consists of three major components that differentiate it from conventional therapy: i) the use of a

restrictive mitt, ii)repetitive training with shaping and task activities, and iii) the transfer package [5]. As opposed to the original parameters of CIMT (i.e. 6 hours a day, for 3 weeks for low functioning PwS), we have used an mCMT protocol with less intensity in terms of application parameters (see below).

However, components of the CIMT were strictly followed: i) all PwS were instructed to wear restrictive mitt during the therapy sessions and 90% of the waking hours except during activities that are not safe or involving hygiene (i.e. toileting, bathing, etc,.), ii) all PwS received a repetitive training with shaping and task activities depending on their capabilities and therapy goals, iii) transfer package was applied and followed for all PwS. Each mCIMT protocol was decided by the leading (ENK) and corresponding authors (BEH) after the baseline evaluation to prevent bias towards groups.

i. **mCIMT alone:** The mCIMT group received an hour-long rehabilitation three times per week, for 5 weeks (15 sessions in total). mCIMT protocol included all three aspects and their sub-components of the CIMT protocol[4–6]. The mCIMT protocol was customized for each participant in the study. Supplementary Figure 1 shows some examples of shaping and task activities used during the intervention.

ii. **mCIMT +sham iTBS:** This group received a sham iTBS on the impaired M1 cortex 5 minutes before mCIMT. Sham application was delivered by flipping over the coil since the output of the flipped side was much lower[29]. Also, sham stimulation intensity was set at 20% of the MSO, to create a sound like the real iTBS.

iii. **mCIMT+iTBS:** Participants in the mCIMT + iTBS groups were treated with the combination of real iTBS and mCIMT. Three-minute iTBS consisting of 600-pulses (50 Hz frequency, 200 ms intervals) was applied on the motor hot spot on the

impaired M1, for 5 minutes[30]. Stimulation intensity was set at 80% of the RMT. iTBS was applied every other day as defined in a previous study[31].

Statistical Analysis

The sample size analysis was performed with GPower (v3.1). The necessary sample size was determined to be 15, taking into account three repeated measurements within three groups, with a power of 90% and a margin of error of 5%, while considering the FMT-UE MCID value of 12.4 and a standard deviation of 5.0[18].

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Version 20 (IBM SPSS Statistics, New York, USA). Descriptive statistics are reported as means ± standard deviations (SDs) for continuous variables and as numbers and frequencies for binary and categorical variables. Intention-to-treat (ITT) analysis was used to analyze participants who dropped out of the study. ITT analysis was performed using the "Expectation Maximization (EM)" method since the study population was less than <30 and therefore data were classified as non-parametric data. The comparison of the groups at pre-treatment was conducted by using the Mann-Whitney U Test since the data were non-parametric. Friedmann Test was used within-group analysis for repeated measures, whereas before-after analysis within groups was conducted using the Wilcoxon Signed Rank Test. Changes in different times between the groups were analyzed by performing a Kruskal-Wallis Test on the difference between timelines (e.g. post-pre). The statistical significance was set at an alpha level of 0.05 ($p<0.05$).

RESULTS

In total 15 PwS (age 66.3 ± 9.2 years (mean ± SD), 53% female) were included in the study. The flowchart of the study population is presented in Figure 1. The reason for refusal from the participants or their caregivers was logistical concerns such as long travel distances from their homes to the study site.

[Figure 1 here]

The sociodemographic, physical, and disease-related data of the study groups are presented in Table 1. There was no difference in any parameter between the groups ($p>0.05$). The groups were also comparable in both primary and secondary outcome scores at the T1 ($p>0.05$). However, a wide inter-subject variability in RMT was evident, which also affected other electrophysiological measurements (see Supplemental Material). The detailed results regarding the inter-subject variability in RMT are provided in the next sub-heading.

Of note, no adverse effect was reported during the course of the study.

a. Primary Outcome Measures

Friedmann's Test revealed that FMT-EU, AUS, and HWS of MAL-28, and FAS of WFMT significantly increased in each group (Table 2). The post-hoc analysis showed that for the FMT-UE motor score, there was a significant difference between T1 and T2 assessments and between T1 and T3 assessments in each group ($p<0.05$). However, there was no significance between T2 and T3 assessments in groups. The mCIMT (meanΔ=13.20) points and mCIMT+iTBS (meanΔ=12.40) groups reached the MCID value for FMT-UE after the 15 sessions. The MCID value was not achieved after 10 sessions (See Table 2). The effect size of iTBS was calculated as *Cohen's f*=0.18.

In electrophysiological measurements, no statistically significant change was detected within any group ($p>0.05$) (Table 2). In between-group measurements, a statistically significant difference was found in favor of the mCIMT+iTBS group ($p<0.05$). The changes in electrophysiological measurements are also shown in Figure 2.

[Figure 2 here]

Given the significant inter-subject variability observed in RMT (as detailed in Supplementary Material), additional analyses were undertaken to enhance result reliability through outlier removal in the variables. Within-group analysis (i.e. Friedmann Test) revealed that there was no difference in MEPs ($p=0.05$, $p=0.174$, and $p=0.472$ for mCIMT, mCIMT+sham iTBS, and mCIMT+iTBS, respectively), in RMT ($p=0.09$, $p=0.135$, and $p=0.472$ for mCIMT, mCIMT+sham iTBS, and mCIMT+iTBS, respectively), in ICF ($p=0.05$, $p=0.127$, and $p=0.779$ for mCIMT, mCIMT+sham iTBS, and mCIMT+iTBS, respectively), in SICI ($p=0.135$, $p=0.174$, and $p=0.472$ for mCIMT, mCIMT+sham iTBS, and mCIMT+iTBS, respectively). Between-group analysis (i.e. Kruskal-Wallis Test) revealed that there was no difference in any of the electrophysiological measurements between the groups in T2-T1 assessments ($p>0.05$ for all) and T3-T2 assessments ($p>0.05$ for all). However, the improvements from T1 to T3 assessments were significantly different between the groups in ICF parameters ($p=0.046$) in favor of mCIMT+iTBS group.

b. Secondary Outcome Measures

Table 3 represents the change in secondary outcome measures in each group over time. Even though there were no statistically significant differences within and between-group comparisons in the FIM – Self-care score, the MCID score for FIM was achieved only in the mCIMT + iTBS group (meanΔ=11.20 points). For the FAS of WFMT, there was no difference between T1 and T_2 in mCIMT ($p>0.05$) and mCIMT + sham iTBS ($p>0.05$),

whereas the mCIMT + iTBS group had a significant difference ($p<0.05$). Importantly, there was a significant difference between T1 and T3 assessments in all study groups. Interestingly, the mCIMT group did not have a significant increase in FAS between T2 and T3 assessment, whereas mCIMT + sham iTBS and mCIMT + iTBS groups reached the significance ($p<0.05$). The performance time in WFMT in the mCIMT + iTBS group both significantly decreased between T1 and T3 assessments and T2 to T3 assessments ($p<0.05$), whereas no difference was found between the T1 to T2 assessments. Post-hoc analysis also showed that the strength parameter in WFMT in the mCIMT + iTBS group did not significantly increase from T1 to T2 assessment, and from T2 to T3 assessment, most importantly, it significantly increased from T1 to the T3 assessment ($p<0.05$).

DISCUSSION

In our study investigating the effect of an adjunct iTBS application to the mCIMT (1 hour/day, 3 days/week, 5 weeks) in PwS, all groups had statistically increased UE motor function. However, mCIMT and mCIMT+iTBS groups have also achieved MCID for FMT-UE. Of note, the effect size of iTBS in increasing motor function (Cohen's *f*) was only 0.18, which was considered a small to medium effect size[32]. Additionally, iTBS may enhance the effect of mCIMT by increasing the cortical excitability, speed, and strength of the impaired UE as well as decreasing the disability in daily life self-care activities.

Smith et al. [33] reported that the use of mCIMT for 1 to 1.5 hours a day, 3 times a week for 6 weeks increases the motor function in lower UE functioning PwS. In line with our first aim, it was found that even an mCIMT protocol consisting of 1 hour/day, 3 days/week for 5 weeks of therapy could both statistically and clinically increase the motor function in UE and lead to motor recovery in low-functioning PwS. Therefore, we suggest further research to follow our protocol since it was less intense and was of shorter duration. Notably,

the findings from earlier studies[34–37] and our results may indicate that iTBS and mCIMT should be administered for at least 15 sessions in order to obtain clinically meaningful recovery in PwS with moderate to severe UE impairments. In contrast to the original protocol, iTBS should not be stopped after the 10th session[30].

In the present study, we observed that iTBS was not superior to the sham or therapy alone in motor function and recovery. Since this is the first study to investigate the effect of iTBS as an adjunct to the mCIMT in PwS, we have not had the opportunity to compare our findings with those of previous research. However, three recent meta-analyses have indicated that the iTBS led to a greater improvement in UE recovery, assessed by FMA-UE, compared to control groups[35,36,38]. One of these meta-analyses demonstrated a significant increase in FMA-UE scores with iTBS application only in the chronic phase[35]. The other meta-analyses[36,38] found that iTBS only "slightly" augmented the treatment effects, especially in the acute phase (between 2.7 - 3.20 points), which was significantly less than the MCID value for FMA-UE[18]. However, an MCID value of 12.4 points was achieved in the MCIMT alone and mCIMT + iTBS groups of the current study, but there were no between-group differences. The difference between the findings of our study and these meta-analyses could potentially be attributed to a ceiling effect.

In other words, it is possible that PwS with moderate-to-severe UE hemiparesis may have already maximized their recovery potential with mCIMT, given that mCIMT has shown superiority over conventional rehabilitation techniques[4]. Therefore, mCIMT may potentially limit the added benefits of iTBS, as mCIMT itself represents a highly effective rehabilitation approach [1,39]. It is like trying to pour more water into a glass that is already full. It is also reasonable to assume that conventional therapies may not enable PwS to reach their full potential and thus, iTBS could offer supplementary benefits as an adjunct therapy.

Sung et al.[40] showed that iTBS in addition to the conventional therapy significantly improved the performance time assessed within the WMFT compared to sham iTBS. The same ceiling effect may also be the reason for the insignificant between-group findings in our study since there was no other evident difference between our study and the study by Sung et al.[40]. Malcolm et al.[41] also applied excitatory rTMS to ipsilesional M1 along with the mCIMT in PwS and reported that although rTMS had significant within-group differences, there was no difference between real and sham rTMS[41].

The authors seek to explore the seemingly, albeit insignificant, baseline differences in the performance time between the groups. It's imperative to highlight that a 20-second disparity in performance time among low-functioning PwS isn't deemed significant. It's crucial to acknowledge that such a difference could arise from one individual's incapacity to execute two specific tasks on the WMFT, thereby accumulating a score of 120 seconds (240 seconds in total) for those tasks. This would result in an increase for about 16 seconds in the performance time. Considering the fine motor skills and hand function of low-functioning PwS and WMFT item, this scenario is probable. This notion could also be supported by the findings of Huang et al. [42]. Similarly to the current study, Huang et al. [42] also included PwS with limited UE function and despite having 16 minute baseline difference in performance time between groups, there was no statistical significance.

There were no between or within-group differences in RMT, MEP, or SICI whereas a significant between-group difference for ICF was found in favor of the mCIMT + iTBS group in the present study. An earlier study[43] suggested that CIMT did not significantly improve the RMT. Later, another study by El-Helow et al.[44] showed that RMT was significantly increased after mCIMT in acute stroke. The difference between the findings in RMT could have originated from the difference between the study populations. Our study and the study by Wittenberg et al.[43] both included the PwS who had the incident in the last 12 months,

while El-Helow et al.[44] recruited PwS within the first two weeks after the incident. Another reason could be the duration of the rehabilitation in these studies. El-Helow et al.[44] reported significant changes in RMT after the original CIMT protocol which was 6 hours per day for 2 weeks. Therefore, it may be reasonable to expect significant changes in RMT and other cortical excitability measures after more intensive forms of CIMT and/or in PwS who are in the acute stages of the stroke.

The electrophysiological measurements of this study exhibited wide inter-individual variability, which is a well-known and highly discussed problem in the field [45,46]. This variability may arise from biological factors such as gender, age, skull thickness, etc [45,47]. Thus, it is reasonable to expect variability in the current study as a result of differences in gender and age among the participants. However, our results on the electrophysiological measurements did not change after the removal of this variability upon sensitivity analysis.

The major strength of this study is that it is the first to explore the effect of iTBS as an adjunct to mCIMT. Moreover, we have shown that PwS were still able to achieve MCID value for primary outcome measure even if it was applied just for an hour and three times a week. Similarly, iTBS was still able to provide small benefits when it was not applied daily as suggested in its original protocol and it was still able to provide MCID value for both motor function and participation in daily life activities. We believe that these findings may have major clinical and research implications.

Study Limitations

This study had some limitations. First of all, we were only able to recruit a small participant population since the inclusion criteria for both iTBS and mCIMT were constraining[48,49]. However, we have been able to reach a minimum number of participants as determined by the parameters defined for power analysis in the statistical analysis section.

Additionally, repeated measurements further increase the study power[48]. Second, due to the nature of the stroke and the small sample size, the variability in some parameters such as electrophysiological measurements was high. Lastly, we were unable to blind the assessor due to pandemic conditions. However, to prevent bias towards groups, each mCIMT protocol has been tailored by the two authors in this study according to the needs of participants and the protocol has been strictly followed by the leading author.

Conclusions

Our findings suggested that mCIMT (1 hour/day, 3 days/week, 5 weeks) increased the UE motor function in low-functioning PwS. iTBS applied on intermittent days provided some additional benefits to mCIMT such as improving cortical excitability, UE speed, and impaired arm strength as well as achieving clinically significant functionality in self-care activities. The findings obtained from this study formed an important basis for future research in terms of iTBS and mCIMT application doses. However, due to the restrictive nature of mCIMT and iTBS application eligibility criteria, the generalizability of our findings is limited. Therefore, we suggest for future research to include participants beyond our study (e.g. PwS with high spasticity).

Declaration of Conflicting Interest: None.

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Figure Legends

Figure 1. Flowchart of the study population.

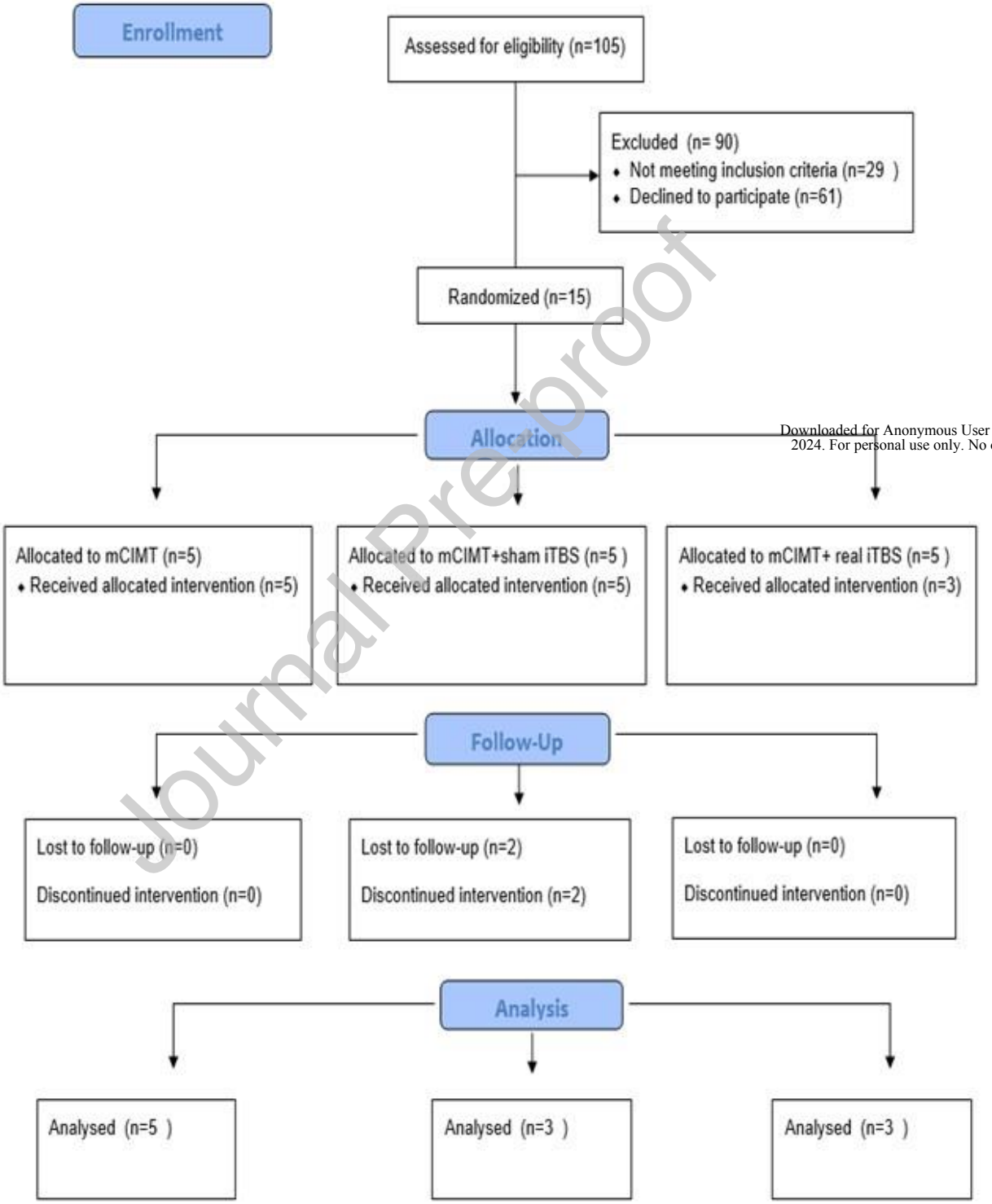

Figure 2. Changes in electrophysiological measurements during the intervention. a) Resting motor threshold, b) Motor-evoked potentials, c) Intracortical facilitation, d) Short intracortical inhibition. T1: Baseline; T2: Evaluations after 10th session; T3: Post-assessments.

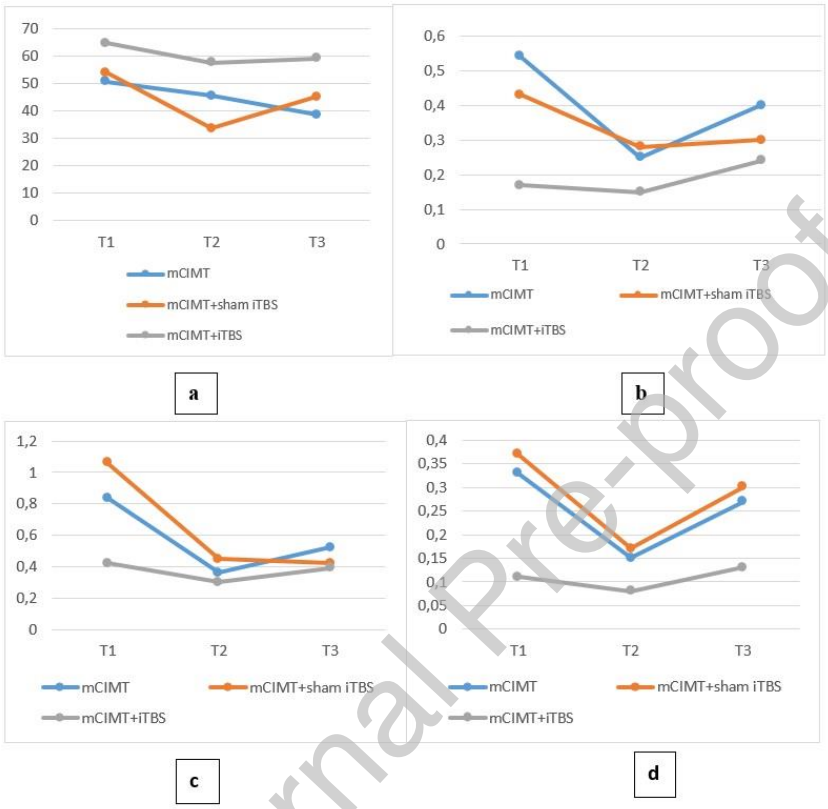

Table 1. Sociodemographic and disease-related data distribution by groups.

	mCIMT (n=5)	mCIMT+sham iTBS (n=5)	mCIMT+iTBS (n=5)	*p* value
Age (years)	68.8 ± 5.9	60.6 ± 10.2	69.4 ± 9.9	ns
Gender				
Female (n.%)	3 (60.0%)	2 (40.0%)	3 (60.0%)	ns
Male (n.%)	2 (40.0%)	3 (60.0%)	2 (40.0%)	
Education				
Illiterate (n.%)	1 (20.0%)	-	2 (40.0%)	
Primary school (n.%)	2 (40.0%)	3 (60.0%)	3 (60.0%)	ns
Middle school (n.%)	-	1 (20.0%)	-	
High school (n.%)	2 (40.0%)	1 (20.0%)	-	
Body-Mass Index (kg/m^2)	30.2 ± 5.3	27.1 ± 4.8	27.8 ± 3.6	ns
Arterial Infarction				
ACA (n.%)	-	1 (20.0%)	1 (20.0%)	
MCA (n.%)	2 (40.0%)	4 (80.0%)	1 (20.0%)	ns
PCA (n.%)	3 (60.0%)	-	3 (60.0%)	
Disease duration (weeks)	19.2 ± 16.1	22.6 ± 17.6	17.6 ± 10.6	ns
Impaired extremity				
Right (n.%)	1 (20.0%)	1 (20.0%)	2 (40.0%)	ns
Left (n.%)	4 (80.0%)	4 (80.0%)	3 (60.0%)	

ACA: Anterior Cerebral Artery. MCA: Middle Cerebral Artery. PCA: Posterior Cerebral Artery. ns: no significance.

Table 2. Results of primary outcome measures in each group.

	mCIMT (n=5) mean±SD				**mCIMT+sham iTBS (n=5) mean±SD**				**mCIMT+iTBS (n=5) mean±SD**						
	T1 Assessment	T_2 Assessment	T3 Assessment	*p-value* ∑	T1 Assessment	T_2 Assessment	T3 Assessment	*p-value* ∑	T1 Assessment	T_2 Assessment	T3 Assessment	*p-value* ∑	*p-value*¥	*p-value* Ω	*p-value*α
FMT-UE															
Motor	39.4 ± 5.9	45.9± 4.7	52.6± 8.4	**0.02**	42.0 ± 13.7	49.8± 13.1	52.6± 12.8	**0.02**	38.8 ± 12.8	47.2± 14.6	51.20 ±13.78	**0.02**	ns	ns	ns
Sensation	9.6 ± 2.1	9.5±1.0	11.0± 1.2	Ns	8.0 ± 2.8	8.4±3.1	9.5±2.0	Ns	7.8 ± 3.6	10.8± 0.8	11.20 ±0.84	Ns			
PROM	20.8 ± 5.1	23.5± 0.5	22.4± 1.8		20.8 ± 1.9	21.8± 1.3	21.6± 1.4		20.6 ± 5.3	23.0± 1.7	23.20 ±1.79				
Pain	20.6 ± 4.9	22.5± 1.7	23.0± 1.2		18.2 ± 3.7	20.9± 1.9	21.1± 1.2		19.8 ± 5.2	22.4± 2.1	22.00 ±3.39				
EM															
RMT	50.9 ± 7.5	45.6± 14.8	38.8± 8.4	ns	54.2 ±13.6	33.8± 21.6	45.4± 17.6	0.056	65.0 ± 13.0	57.8± 20.9	59.2± 21.2	ns	ns	ns	ns
MEPs	0.5 ± 0.4	0.3±0.1	0.4±0.3		0.4 ± 0.4	0.3±0.4	0.3±0.5		0.2 ± 0.1	0.2±0.1	0.2±0.2			ns	
ICF	0.8 ± 0.5	0.4±0.2	0.5±0.4		1.1 ± 1.4	0.5±0.5	0.4±0.7	ns	0.4 ± 0.4	0.3±0.1	0.4±0.3			**0.03**	
SICI	0.3 ± 0.2	0.2±0.1	0.3±0.2		0.4 ± 0.3	0.2±0.2	0.3±0.4		0.1 ± 0.1	0.1±0.0	0.1±0.1			ns	

Bold numbers indicate significance ($p<0.05$). FMT-UE: Fugl-Meyet Test – Upper Extremity. PROm: Passive Range of Motion. EM: Electrophysiological Measurements. RMT: Resting Motor Threshold. MEPs: Motor Evoked Potentials. ICF: Intracortical Facilitation. SICI: Short Intracortical Inhibition. ns: No significance.

∑**:** Within-group comparisons – repeated measures (Friedmann's Test).

¥: Between groups comparison – from T1 to T_2 (analyze of the difference with Kruskal Wallis Test).

Ω: Between groups comparison – from T1 to T3 assessment (analysis of the difference with Kruskal Wallis Test).

α: Between groups comparison – from T_2 to T3 assessment (analysis of the difference with Kruskal Wallis Test).

Table 3. Results of secondary outcome measures in each group.

	mCIMT (n=5) mean±SD				**mCIMT+sham iTBS (n=5) mean±SD**				**mCIMT+iTBS (n=5) mean±SD**						
	T1 Assessment	T_2 Assessment	T3 Assessment	*p-value*	T1 Assessment	T_2 Assessment	T3 Assessment	*p-value*	T1 Assessment	T_2 Assessment	T3 Assessment	*p-value*	***p* value ¥**	***p* value Ω**	***p* value α**
MAL-28															
AUS	0.7 ± 0.5	-	3.2±0.9	**0.043***	0.5 ± 0.5	-	2.6±1.6	**0.043***	0.4 ± 0.3	-	2.8±1.8	**0.043***	-	0.756	-
HWS	0.8 ± 0.7	-	3.2±0.9	**0.043***	0.4 ± 0.5	-	2.4±1.2	**0.043***	0.4 ± 0.3	-	2.7±1.8	**0.042***	-	0.594	-
WFMT															
FAS	3.3 ± 0.4	3.8±0.4	4.2±0.3	**0.021** Σ	3.1 ± 1.1	3.3±0.9	3.6±0.9	**0.015** Σ	3.3 ± 1.1	3.7±1.1	3.9±1.1	**0.007** Σ	ns	ns	ns
Performance Time	12.4 ± 8.1	13.1±9.6	7.9±5.3	ns Σ	36.2 ± 33.2	34.5±30.2	27.2±23.5	ns Σ	32.8 ± 20.2	25.7±27.6	23.7±26.3	**0.015** Σ	ns	ns	ns
Impaired Arm Strength	2.0 ± 1.7	1.6±0.5	2.6±1.4	ns Σ	1.7 ± 1.5	2.2±1.2	3.4±2.0	ns Σ	1.7 ± 2.1	2.5±2.0	3.3±2.8	**0.014** Σ	ns	ns	ns
Impaired Handgrip Strength	8.3 ± 6.6	11.1±8.2	13.4±9.9	ns Σ	9.8 ± 9.6	5.3±4.8	10.6±8.5	ns Σ	8.2 ± 8.1	5.6±6.0	10.3±9.9	ns Σ	ns	ns	ns
Non-Impaired Handgrip Strength	19.7 ± 9.6	18.8±7.4	24.0±13.6	ns Σ	25.5 ± 13.6	15.2±5.2	26.9±9.5	ns Σ	16.6 ± 7.9	15.6±4.6	22.4±10.5	ns Σ	ns	ns	ns
FIM-Self Care	24.0 ± 13.1	-	31.8±10.1	ns*	26.1 ± 14.8	-	34.9±3.9	ns*	19.8 ± 7.7	-	30.4±11.0	ns*	-	ns	-

Bold numbers indicate significance ($p<0.05$). FIM: Functional Independence Measure. MAL-28: Motor Activity Log-28. ROM: Range of Motion. AUS: Amount of Use Scale. HWS: How-Well Scale. FAS: Functional Ability Scale. Wolf Motor Function Test. FAS: Functional Ability Scale. ns: No significance.

*: Within-group comparisons – from post to T1 assessments (Wilcoxon Test). ∑: Within-group comparisons – repeated measures (Friedmann's Test). ¥: Between groups comparison – from T1 to T_2 (analyze of the difference with Kruskal Wallis Test). Ω: Between groups comparison – from T1 to T3 assessment (analysis of the difference with Kruskal Wallis Test).

α: Between groups comparison – from T_2 to T3 assessment (analysis of the difference with Kruskal Wallis Test).

Graphical abstract