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Early transcranial direct current stimulation with modified constraint-induced movement therapy for motor and functional upper limb recovery in hospitalized patients with stroke: A randomized, multicentre, double-blind, clinical trial☆

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ABSTRACT

Background: Constraint-induced movement therapy (CIMT) and transcranial direct current stimulation (tDCS) are used to reduce interhemispheric imbalance after stroke, which is why the combination of these therapies has been used for neurological recovery, but not in the acute phase.
Objectives: To evaluate the effectiveness of combining active or sham bihemispheric tDCS with modified CIMT (mCIMT) for the recovery of the Upper Limb (UL) in hospitalized patients with acute and subacute stroke.
Methods: This randomized controlled, double-blind, placebo-controlled, parallel group clinical trial was executed between September 2018 to March 2021 recruited 70 patients. The patients were randomized to one of two groups to receive treatment for 7 consecutive days, which included 20 min of active or sham bihemispheric tDCS daily (anodal ipsilesional and cathodal contralesional), with an mCIMT protocol. The primary outcome was the difference in the evolution of motor and functional upper limb recovery with assessment on days 0, 5, 7, 10 and 90. The secondary outcomes were independence in activities of daily living (ADL) and quality of life.
Results: The active group presented a statistically significant gap compared to the simulated group throughout the trend in the scores of the FMA (motor function and joint pain) and WMFT (functional ability and weight to box) ($p < 0.05$) and showed a minimal clinically important difference (FMA: difference between groups of 4.9 points [CI: 0.007- 9.799]; WMFT: difference between groups of 6.54 points [CI: 1.10-14.15]). In the secondary outcomes, there was a significant difference between the groups in ADL independence (Functional Independence Measure: difference of 8.63 [CI: 1.37-18.64]) and perceived recovery of quality of life evaluated at 90 days ($p = 0.0176$).

Abbreviations: CIMT, Constraint-induced movement therapy; tDCS, Transcranial direct current stimulation; mCIMT, Modified constraint-induced movement therapy; UL, Upper Limb; ADL, Activities of daily living; FMA, Fugl meyer assessment; NIBS, Noninvasive brain stimulation; LTP, Long-Term Potentiation; LTD, Long-Term Depression; rTMS, Repetitive transcranial magnetic stimulation; RCT, Randomized clinical trials; FME-UE, Fugl Meyer Assessment- upper extremity; WMFT, Wolf Motor Function Test; FIM, Functional Independence Measure; MCID, Minimal clinically important difference.

☆ The Ethics Committee of the HCUCH (OAIC number 849/16) approved this study. All participants provided informed consent and their safety and respect were protected. Written informed consent was obtained from all the participants from both participating hospitals. No changes were observed during the course of the study.

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Conclusions: Combining mCIMT with bihemispheric tDCS in patients hospitalized with acute-subacute stroke allows us to maximize the motor and functional recovery of the paretic upper limb in the early stages and independence in ADL, maintaining the effects over time.

1. Introduction

Stroke is one of the main causes of serious long-term disability, deterioration of the quality of life, and socioeconomic costs [1,2].Hemiparesis of the upper limb (UL) is one of the main sequelae of stroke (present in 80% of patients). Although rehabilitation strategies have undergone significant development in recent years, motor and functional recovery remain insufficient; therefore, it is necessary to continue investigating new approaches.

Constraint-induced movement therapy (CIMT) is one of the approaches with the most scientific evidence in the recovery of the upper limb poststroke in its different evolutionary stages [3]. The principle of CIMT is based on the notion that by increasing the use of the affected UL and reducing the use of the unaffected upper limb, abnormal transcallosal inhibition generated by this region on its homologous area in the affected hemisphere can be decreased, thus increasing ipsilesional activation and improving the clinical result [4]. In addition, functional neuroimaging studies have found that there is an alteration in excitability and interhemispheric balance after stroke; for example, hypoactivity in the affected hemisphere and hyperactivity in the unaffected hemisphere in patients with subacute/chronic stroke and moderate motor deficit would reduce the possibility of achieving greater recovery [5,6].

Transcranial direct current stimulation (tDCS) is a type of noninvasive brain stimulation (NIBS) that consists of applying low-intensity electrical current directly to the scalp [7]. tDCS has been used based on 2 two fundamental principles: to reduce the alteration in the interhemispheric balance (modifying the resting membrane potential of neurons) and to improve brain plasticity (Long-Term Potentiation-LTP, Long-Term Depression-LTD, etc.) [7,8]. For motor recovery the stimulated area is usually the M1 primary motor cortex, with the unihemispheric or bihemispheric approaches being the most commonly used.

The bihemispheric approach seeks to increase activation in the affected hemisphere and decrease hyperactivity of the unaffected hemisphere (due to the release of reciprocal inhibition). The influence of the contralesional hemisphere on functional results was already described in the first studies by Oliveri et al. [9,10] who found positive results on manifestations of neglect, when applying a transient repetitive transcranial magnetic stimulation (rTMS) to the unaffected hemisphere, decreasing its hyperactivity and the magnitude of neglect as expressed in the number of errors.

Randomized clinical trials (RCT) have shown that combining tDCS with neurorehabilitation strategies can increase motor recovery [11–13]. Most studies that have combined CIMT with tDCS have been performed in chronic patients [14–16], and to our knowledge, only one pilot RCT by Andrade et al. [17] has evaluated the effects of these approaches in subacute patients (as the early stages of stroke are crucial to obtaining better results), with good results in motor recovery in patients with severe stroke. However, the potential benefits of tDCS remain controversial and these may vary depending on the selected assessment, stage of stroke, and associated therapy [18,19]. In the case of acute intervention the effects are more limited and controversial, for example, Yagüe did not observed significant changes in patients with acute stroke and severe motor impairment [20], but Shibata found durable effects on functional recovery [21].

Therefore, we conducted a multicenter RCT to compare the effects of the combination of active or sham tDCS with modified CIMT (mCIMT) on motor and functional recovery of the UL in patients hospitalized for acute-subacute stroke. The hypothesis was that the active group would obtain better motor and functional results than the sham group, with differences maintained over time.

2. Methodology

2.1. Study design and participants

A randomized, double-blind, parallel-group clinical trial was conducted in two hospitals in the northern area of Santiago, Chile: Hospital Clínico Universidad de Chile (HCUCH) and Hospital San José (HSJ). Hospitalized adults aged 18 years and older, with an unihemispheric stroke, 2–14 days since the time of stroke, ischemic or hemorrhagic stroke, with UL hemiparesis (at least 20° of active wrist extension and 10° of finger extension), and who signed an informed consent form were included. Patients with the following were excluded: severe aphasia (score of $\geq$2 points in the National Institute of Health Stroke Score (NIHSS) language item assessment), moderate to severe cognitive impairment (score of $\leq$15 points in a Mini-Mental State Examination assessment), shoulder subluxation or shoulder pain >4 points in the numerical visual scale of pain, uncontrolled epilepsy or epilepsy episode in the last 3 months, metallic implants, pregnancy, or any condition that, according to medical judgment, may hinder the correct development of treatment.

This study is accordance with Consolidated Standards of Reporting Trials (CONSORT) and Template for intervention description and replication (TIDieR) guidelines.

2.2. Interventions

A group of 12 occupational therapists (six in each hospital) previously trained in the protocol were in charge of carrying out the interventions; they did not know the group assigned to the patient and did not perform the assessment.

The patients were randomly assigned to one of the following treatment groups: (i) control group, sham bihemispheric tDCS combined with mCIMT or (ii) experimental group, active bihemispheric tDCS combined with mCIMT. A protocol of seven consecutive days was used in both groups and included the following interventions.

1. mCIMT: considered 2 main elements.
   a) Restriction of mobility of the unaffected hand: Patients had to use a constraint mitt for 6 h per day, which prevented only finger movement, leaving the wrist-elbow-shoulder joint free. The use of the mitt coincided with the training schedules of the affected UL and could be removed for hygiene activities, showering, eating or any activity in which wearing the mitt posed a risk to patient safety.

b) Training of the affected UL: Patients underwent two 1-h sessions of intensive and individualized training of the affected UL every day, separated by at least 2 h, and performed by an occupational therapist (14 sessions total). A task-oriented approach was used.

The duration and intensity of the protocol of this mCIMT was chosen in relation to the feasibility of implementing it during the hospitalization period of the patients, which is on average 14 days, and considering the good evidence presented by both the original protocol and the modified ones [22].

2. tDCS

For the application of active or sham tDCS, a bihemispheric montage was used, which was applied during the first 20 min of one of the two UL training sessions (seven tDCS sessions in total). The montage began with the installation of a pair of 25 cm2 surface sponge electrodes soaked in saline solution and connected to a current generated by a battery. To keep the therapist and patient masked, the tDCS device was previously configured to provide active or sham stimulation (the NE STARSTIM tCS® Barcelona, Spain device was used), with the following modalities.

a) Active tDCS: The location of the electrodes was anodic on the affected M1 (C3/C4) and cathodic on the unaffected M1 (according to the 10/20 electroencephalography (EEG) system), with a duration of 20 min and an intensity of 2 mA (30 s ramp up and down).
b) Sham tDCS: The same stimulation parameters as the active group were used, but the device was deactivated after 30 s, which ensured that the patient could feel a slight initial tingling, which was a requirement for masking.

3. General Procedures.

During the days in which the protocol was applied, patients received their regular rehabilitation sessions (physical therapy, speech therapy). When the patient was discharged before the end of the protocol, he or she had to continue attending the corresponding hospital daily to complete the 7-day period and follow-up evaluations. In this case, he or she was asked to record compliance with the use of the constraint mitt and the assigned activities.

The complete intervention protocol is available with illustrations in the Supplementary Material 1, and the study protocol has been published [23].

2.3. Evaluation of results

A group of four occupational therapists previously trained in the outcome assessment were in charge of carrying out the evaluations. They did not know the group assigned to the patient and applied the first evaluation after being informed by the recruiter (once the patient signed the informed consent form).

The primary outcome was the difference in the evolution of motor and functional UL recovery, evaluated using the Fugl Meyer Assessment-upper extremity (FMA-UE) [24], which includes: motor function ranging from 0 to 66 points, sensory function from 0 to 12 points, joint range of movement from 0 to 24 points, and joint pain from 0 to 24 points; and Wolf Motor Function Test (WMFT) [25], which includes WMFT functional ability score, WMFT time and WMFT strength (grip strength and weight to box), applied on days 0, 5, 7, 10 and 90. Secondary outcomes were independence in activities of daily living (ADL) evaluated using the Functional Independence Measure (FIM) [26] on days 0, 5, 7, 10, and 90; and quality of life as evaluated using the Stroke Impact Scale (SIS) [27] questionnaire on day 90. The following demographic variables were collected: age, sex, education, and employment. Finally, we administered a questionnaire to assess the level of satisfaction, adverse effects, and the results of the masking on day 7 (see Supplementary Material 2).

2.4. Randomization, blinding and allocation

Patients were assigned to active or sham groups using block randomization. The person responsible for obtaining informed consent notified the person in charge of randomization (who did not have contact with the patient or access to the clinical history), who then sent the information of the assigned group to the person in charge of programming the tDCS device via text message. The participants, evaluators and therapists were blinded to group assignment. Statistical analysis was performed by an external person who had no contact with study patients.

2.5. Sample size and statistical analysis

The sample size was calculated in relation to the motor recovery of the UL (evaluated with FMA), taking into account similar RCTs [28,29] and the results obtained by patients treated at HCUCH in order to achieve a difference of 3 points in FMA-UE with a standard deviation of 8.5 per group, and that the active group obtains a minimally clinically important difference (increase of 10 points) [30] at different times. With a statistical power of 80% and a significance level of 5% to one tail, a baseline assessment measurement, and four follow-up assessments (repeated measurement design), the sample size was 56 participants (28 in each group). We compensated for a 25% drop-out rate, therefore, 70 participants were recruited.

Intention-to-treat analyses were used for all outcomes. Mean differences between variables at baseline were assessed using unpaired t tests and Fisher's exact tests. The mean, standard deviation, and confidence intervals were used for descriptive statistics. The evolution of outcomes was evaluated and compared between groups using mixed models. This model presumes that the groups have equal baseline means, which is appropriate for a RCT, and permits estimation in the presence of missing values, which means that all available data are used.

All confidence intervals were 95%, and the significance level was set at 5%. STATA software (version 14.0) was used.

Clinical trial registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT03452254.

3. Results

A total of 1231 patients were evaluated for eligibility between September 2018 and March 2021, of whom 70 met the inclusion criteria to enter the study and were randomized to one of the two groups (Fig. 1).

3.1. Baseline characteristics of the sample

Both groups were similar in terms of demographic data and baseline performance ($p > 0.05$, Table 1). The patients in the sample were mostly men with a mean age of 65 ± 14 years, were actively working, and had 10 years of schooling (10 ± 4 simulated group, 10 ± 3 active group). There was a homogeneous distribution of groups between the two participating hospitals ($p = 0.999$).

Regarding stroke characteristics, the most frequent type was ischemic, with no significant differences in the distribution of the affected hemisphere. In both groups, middle cerebral artery

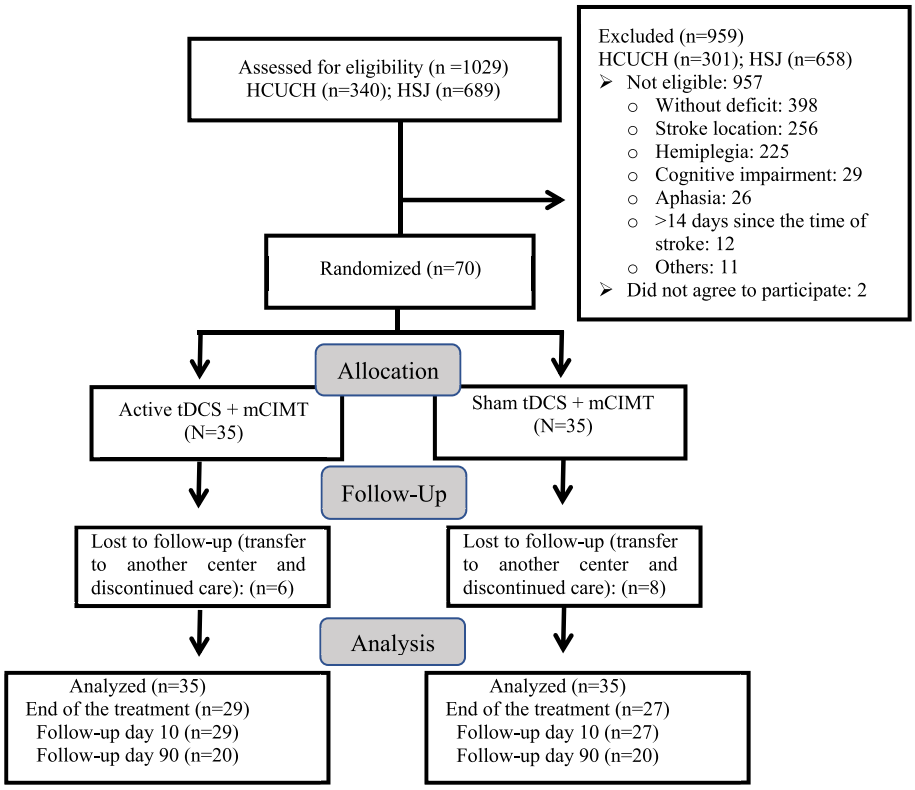

Fig. 1. Consort patient flow chart.

Table 1
Baseline demographic and clinical characteristics.

	Sham Group(n = 35)	Active Group(n = 35)	p value
Age (years), mean SD	65 ± 14	65 ± 12	0.731
Female sex, n %	15 (43%)	18 (51%)	0.632
Hospital, n %			
HCUCH (39)	20 (51%)	19 (49%)	0.999
HSJ (31)	15 (48%)	16 (52%)	
Years of schooling, mean SD	10 ± 4	10 ± 3	0.565
Right handedness, n %	32 (91%)	32 (91%)	0.999
Employed, n %	23 (66%)	26 (74%)	0.4
Stroke type, n %			
Ischemic	34 (97%)	34 (97%)	0.999
Hemorrhagic	1 (3%)	1 (3%)	
Affected side, n %			
Right	21 (60%)	14 (40%)	0.151
Left	14 (40%)	21 (60%)	
Middle cerebral artery affected, n %	30 (86%)	33 (94%)	0.428
Stroke location, n %			
Cortical	21 (60%)	22 (63%)	0.999
Subcortical	12 (34%)	12 (34%)	
Cortico-subcortical	2 (6%)	1 (3%)	
Antidepressant use, n %	2 (6%)	1 (3%)	0.999
Mini-Mental State Examination initial, mean SD	25 ± 3	26 ± 3	0.371
NIHSS initial, mean SD	5 ± 3	5 ± 3	0.969
FMA-UE initial, mean SD	44 ± 13	46 ± 12	0.539
WMFT-FAS initial, mean SD	42 ± 19	44 ± 19	0.656
WMFT time initial (min), mean SD	8,8 ± 9.4	7 ± 8.4	0.373
Total FIM initial, mean SD	69 ± 21	70 ± 22	0.750
Days of hospitalization, mean SD	14 ± 7	14 ± 7	0.999
Days from stroke onset to intervention, mean SD	6 ± 4	6 ± 4	0.533
Use of analgesics	16 (45,7%)	15 (42,7%)	0.81

HCUCH= Hospital Clínico Universidad de Chile. HSJ: Hospital San José. SD: Standard deviation. NIHSS, National Institute of Health Stroke Score; FMA-UE, Fugl Meyer Assessment upper extremity; WMFT-FAS, Wolf Motor Function Test-Functional Ability Score; FIM, Functional Independence Measure.

compromise was affected the most, with the most common cause of stroke being atherothrombosis (p = 0.134).

The baseline results of the main outcomes demonstrated that the patients began with moderate motor and functional deficits of

the UL. In addition, they presented a moderate-to-high level of dependence to perform basic ADL, which was measured using the FIM assessment (Table 1).

3.2. Protocol implementation

The patients were hospitalized for a mean of 14 ± 7 days and began their participation in the protocol on a mean of day 6 ± 4, which is considered an acute-subacute evolution time. There were no differences on the day of protocol initiation in either group (day 2 ± 2 sham group, day 2 ± 1 active group, p = 0.755). Of the total sample, 56 patients completed the full protocol (2 h of upper extremity therapy daily and 20 min of tDCS for 7 days). 36 patients completed the protocol during hospitalization and 20 patients completed the protocol on an outpatient basis as they were discharged before completion, with a comparable proportion between groups (34,6% sham group and 36,7% active group, p = 0.873). The pending sessions were completed on an outpatient basis, maintaining the frequency and intensity, and the use of the mitt at home was tracked (verified through a checklist). In both groups, 3 ± 2 functional activities were first targeted.

3.3. Efficacy analysis of the outcomes

3.3.1. Motor and functional recovery of the upper limb

Significant differences in both the FMA (motor function and joint pain) and WMFT (functional ability and weight to box) were observed in both groups during the time (Table 2 and Fig. 2) (p < 0.05), going from a moderate to a mild deficit of the UL. The active group presented a statistically significant gap compared to the simulated group throughout the trend (p < 0.05) and a minimal clinically important difference (MCID) in the FMA-Motor Function (change of at least 10 points) [30,31], increasing by 11 points on day 7 and 12 points on day 90 (the simulated group did not obtain this). In the WMFT-Funtional ability, both groups presented an MCID (positive change of at least 16%) [32], with a greater change observed in the active group (35% versus 32% on day 7). In both groups, there were significant differences in the decrease in FMA-Joint Pain-in the time, but in the active group, joint pain decreased by a mean of 0.89 points more than in the sham group (significant differences, p = 0,029). In addition, there were significant differences in favor of the active group in the WMFT weight to box assessment (p = 0.014, Table 2).

The FMA-Sensory Function improved significantly in both groups in the time, (p < 0.05), but the comparison between groups was not significant (p = 0.125), and FMA-Joint Range of Movement assessment remained constant over time and the treatment effect was not significant.

The WMFT time and grip strength assessment improved significantly in both groups in the time, (p < 0.05), but the comparison between groups was not significant (p = 0.099 and p = 0.174 respectively).

3.4. Improvement in basic activities of daily living

In both groups, independence in basic ADL (total FIM) significantly increased in the time (p < 0.05) and showed an MCID (positive change of at least 17 points) [33], with a greater change observed in the active group (26 points versus 19 points on day 7).

The active group presented a statistically significant gap compared to the simulated group throughout the trend (p = 0.045), reaching at the 90-day assessment scores that indicate high levels of independence, while the simulated group continues to require supervision from another person (Table 2 and Fig. 2).

Table 2
Scores and significance level of outcomes over time.

	Sham Group			Active Group		
		FMA- MOTOR FUNCTION				
day	n	mean	sd	n	mean	sd
0	35	44.0	12.9	35	45.9	12.1
5	28	50.9	11.2	31	54.6	11.0
7	27	53.4	11.5	29	57.2	10.0
10	27	54.9	10.8	29	59.3	8.4
90	20	53.4	9.6	20	58.7	8.0
Slope		0.04				
slope p-value		0.003				
treatment effect		4.90				
treatment effect p-value		0.025				
		FMA-JOINT PAIN				
day	n	mean	sd	n	mean	sd
0	33	22.3	2.5	34	22.5	2.0
5	28	23.0	1.3	31	23.3	1.3
7	27	22.9	2.4	29	23.2	1.5
10	27	20.1	7.6	29	23.4	1.1
90	20	21.3	3.3	20	22.1	2.9
Slope		0.01				
slope p-value		0.022				
treatment effect		0.89				
treatment effect p-value		0.029				
		WMFT- FUNCTIONAL ABILITY				
day	n	mean	sd	n	mean	sd
0	33	42.1	18.6	34	44.1	18.5
5	28	52.4	16.3	31	56.0	17.1
7	27	55.6	16.8	29	59.5	16.7
10	27	56.9	15.5	29	63.5	15.6
Slope		1.80				
slope p-value		0.000				
treatment effect		6.52				
treatment effect p-value		0.047				
		WMFT – WEIGHT TO BOX (kg)				
day	n	mean	sd	n	mean	sd
0	33	1.98	1.40	34	2.39	1.41
5	28	2.64	1.61	31	3.13	1.40
7	27	2.82	1.50	29	3.73	1.39
10	27	3.23	1.62	29	3.97	1.19
Slope		0.15				
slope p-value		0.000				
treatment effect		0.71				
treatment effect p-value		0.014				
		TOTAL FIM				
Day	n	mean	sd	n	mean	sd
0	33	68.6	21.4	34	70.3	21.8
5	28	81.5	24.3	31	90.5	22.2
7	27	87.8	25.1	29	97.1	22.5
10	27	93.9	24.1	29	102.0	22.3
90	20	103.4	20.9	20	113.7	11.4
Slope		0.30				
slope p-value		0.000				
treatment effect		8.63				
treatment effect p-value		0.046				

FMA-UE, Fugl Meyer Assessment upper extremity; WMFT, Wolf Motor Function Test; FIM, Functional Independence Measure.

3.5. Quality of life

In the quality of life evaluation at 90 days, the active group showed higher scores than the sham group in all domains (except in the communication domain), but this difference was not significant. The most affected domains in both the groups were emotions and participation. Regarding the percentage of perceived recovery, the active group reported a mean of 80% recovery versus the simulated group with 60%, with a significant difference (p = 0.0176, Table 3 and Fig. 2).

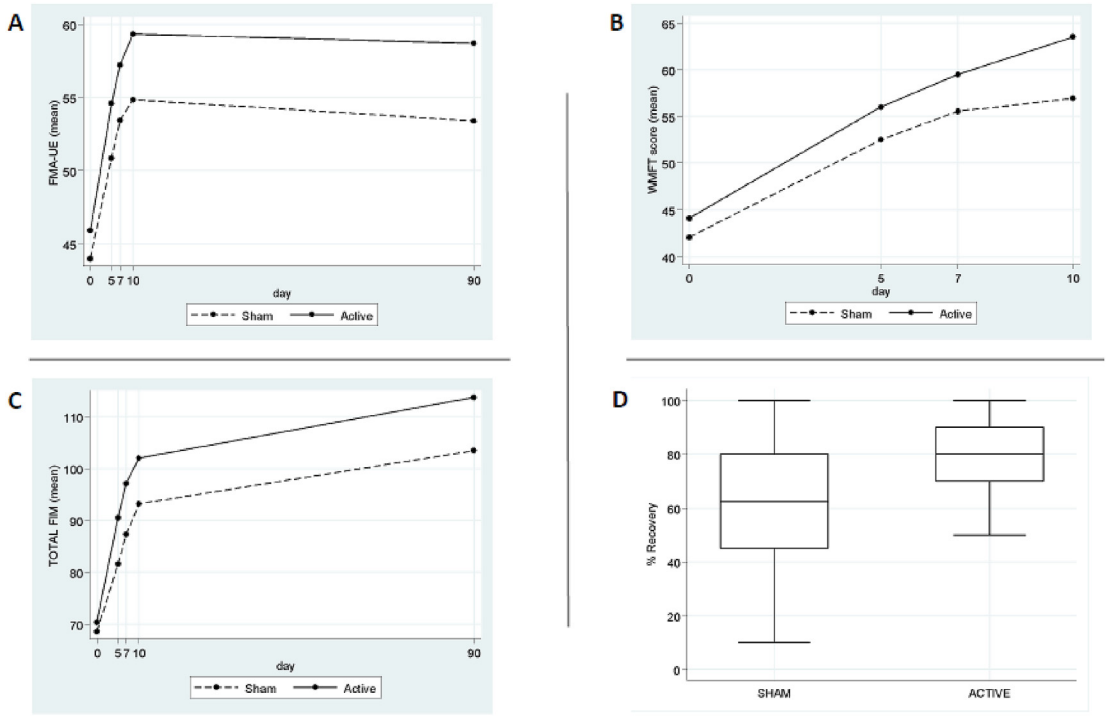

Fig. 2. Outcomes results. (A, C) evaluated on days 0, 5, 7, 10, 90; (B) evaluated on days 0, 5, 7, 10 and (D) evaluated on day 7.

3.6. Adverse effects and stimulation

One hundred percent of the patients responded that they received brain stimulation, indicating the success of blinding. The secondary symptoms were similar in both groups, and 100% of the patients classified them as mild. Thirty-two patients (47%) felt itching (14 from the sham group and 18 from the active group), 17 patients (25%) felt tingling (7 from the sham group and 10 from the active group), 5 patients (7%) had a headache (2 from the sham group and 3 from the active group), 5 patients (7%) felt burning (2 from the sham group and 3 from the active group), but none had redness or burns, and 3 patients (4%) felt fatigued (1 from the simulated group and 2 from the active group).

4. Discussion

The present study is the first to use mCIMT combined with tDCS for UL rehabilitation in patients hospitalized with acute and subacute stroke. The use of mCIMT as the gold-standard therapy in both groups produced significant improvements in mobility, quality of movement, and functionality of the affected UL, in accordance with published studies on this technique in patients with acute and subacute stroke [22]. To our knowledge, this is the first study that uses such a short total duration of the mCIMT protocol (1 week), since most of them have a duration of 2 weeks; which demonstrates the effectiveness of the therapy in shorter times. The combination with active bihemispheric tDCS generated significantly better results than no stimulation, allowing the maximization of the motor and functional recovery of the affected UL in the early stages.

According to previous studies, this is due to brain plasticity mechanisms, such as changes in neuronal-membrane excitability, removal of inhibition, improvement in synaptic transmission (LTP, LTD), allowing the reestablishment of neural circuits involved in the mobility and function of the ULs [34], avoiding compensatory phenomena that tend to establish themselves in the early stages. For example, it has been found that after CIMT, motor output maps in affected hemisphere increased in size by around 40% showing that effective recovery is associated with a gradual normalization of the intensity and degree of activation, moving away from the predominant activation in the unaffected hemisphere [34].

Table 3
Quality of Life results at 90 days.

Outcomes SIS	Sham Group (n = 20)	Active Group (n = 20)	p value
Strength, mean SD	61 ± 23	71 ± 21	0.145
Memory, mean SD	73 ± 27	83 ± 16	0.264
Emotion, mean SD	59 ± 15	63 ± 10	0.056
Communication, mean SD	90 ± 13	87 ± 24	0.463
ADL/IADL, mean SD	74 ± 21	83 ± 16	0.115
Mobility, mean SD	73 ± 25	83 ± 17	0.289
Hand function, mean SD	63 ± 30	73 ± 31	0.301
Participation, mean SD	60 ± 29	60 ± 26	0.956
Total SIS, mean SD	551 ± 145	603 ± 102	0.218
% of Recovery, mean SD	60 ± 28	79 ± 13	0.0176

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; SIS, Stroke Impact Scale.

Unlike other protocols in the acute-subacute stage [11,12], this 7-day protocol was carried out almost entirely during the hospitalization of the patient (14 days of mean hospitalization). On the one hand, this ensures the viability and replicability of this protocol in other hospitals; on the other hand, this allows patients to attain better performance and obtain more tools to return home after hospital discharge. In addition, carrying out a protocol during the patient's hospitalization has its advantages, given that sometimes outpatient rehabilitation processes cannot be fully implemented or include other variables that are difficult to manage. Positive results of implementation include that the patients adhered to the following: the duration of the therapies and the total duration of the protocol, the functional activities and the intensity of the proposed restriction. Although the implementation of mCIMT requires trained human resources and time to carry out individualized therapy, the low cost of mCIMT in terms of materials and its high impact on the performance attained by the patients in this study positions it as the standard therapy of choice in patients with stroke. The intensity of the proposed protocol is related to the recommendation made by Dromerick et al. (2009) [35], who suggested that low-intensity mCIMT, such as that proposed here, would be better than high-intensity mCIMT in patients with acute stroke.

In relation to secondary outcomes, regarding independence in basic ADL, although both groups advanced significantly, only the active group managed to reach the level of independence in their performance, indicating that they did not require a third person for care. We consider that the use of a protocol of activities targeted at functional tasks (which are related to ADL) is important for the achievement of daily skills.

All the above factors may have an impact on reducing the severity of the deficits, the demand for outpatient therapies, and the burden of disease generated by years of living with a disability. If we achieve a lower level of disability in patients who are of productive age, they will have a greater possibility of returning to work and society.

In relation to the quality of life results obtained using the SIS, both groups obtained scores associated with an adequate quality of life during the 90-day follow-up [36]. A significant difference was observed in the active group in relation to the percentage of perceived recovery, which may be consistent with the high scores obtained in the FIM assessment [37]. Although no significant difference was found between the two groups in the subareas, the active group obtained better scores in 7/8 subareas and in the total score, which would be consistent with the better results obtained in the primary outcomes and in the basic ADL.

A limitation of the present study is that the exigent inclusion/exclusion criteria resulted in a low recruitment rate. Although we would like the protocol to have therapeutic application on a larger scale, CIMT can only be applied in patients with active mobility of the upper extremity, and with cognitive abilities that allow them to get involved and understand the objectives of the therapy. However, we believe that the positive results obtained generate a high impact on people who meet the eligibility criteria. Finally, it would have been positive to know the neurophysiological effect in the studied sample, since although some studies have found positive neurophysiological effects when combining tDCS with other approaches, the number of patients evaluated is still low. For example, Bolognini et al., 2011 in a sample of 14 patients found reduction in transcallosal inhibition from the intact to the affected hemisphere and increased corticospinal excitability in the affected hemisphere only in the active tDCS/CIMT group [16] and Lindenberg et al., 2010 in a sample of 20 patients found a stronger activation of intact ipsilesional motor regions during paced movements of the affected limb were found postintervention whereas no significant activation changes were seen in the control group [15].

5. Conclusion

In hospitalized patients with acute-subacute stroke and with a mild to moderate deficit of the UL, the combination of active tDCS with mCIMT for 7 days was significantly better than the sham treatment in terms of the motor and functional performance of the UL as well as ADL independence and the perception of quality of life, thus maximizing recovery in early stages and maintaining the effects over time.

6. Research ethics

The Ethics Committee Hospital Clínico de la Universidad de Chile (OAIC 849/16) approved the project by December 2016. All participants provided informed consent, and their safety and respect were protected.

Data sharing

This information will be available according to the following criteria: study protocol article https://journals.sagepub.com/doi/abs/10.1177/0308022620904339.

The data of participants, without their identification or informed consent form, will be shared after the approval of a proposal made to the research team (with a signed data access agreement).

Consent

All participants provided written informed consent to participate in the study. Consent included authorization to use data, images and videos.

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CRediT authorship contribution statement

Maricel Garrido M: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Evelyn Alvarez E:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Fabrizio Acevedo P:** Methodology, Investigation, Data curation, Writing – review & editing. **Álvaro Moyano V:** Investigation, Data curation, Writing – review & editing. **Natalia Castillo N:** Methodology, Investigation, Data curation, Writing – review & editing. **Gabriel Cavada Ch:** Methodology, Formal analysis, Writing – review & editing.

Declaration of competing interest

All authors received payment for their participation during the execution of the study but not at the design stage or during the writing of the manuscript.

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Appendix A. Supplementary data

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