Synergistic effects of scalp acupuncture and repetitive transcranial magnetic stimulation on cerebral infarction: a randomized controlled trial

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Abstract

Background Presently, there is a need for stroke treatment strategies that combine multiple disciplines, such as neurology, rehabilitation medicine, and traditional medicine. This study investigated the synergistic effects of scalp acupuncture (SA) and repetitive transcranial magnetic stimulation (rTMS) known to be effective for cerebral infarction. Methods This outcome assessor-blinded randomized controlled clinical trial included a per-protocol analysis to compare the efficacy of SA and electromagnetic convergence stimulation (SAEM-CS), which comprises the simultaneous application of low-frequency rTMS, SA, rTMS, and conventional stroke rehabilitation therapy (CSRT) for cerebral infarction patients. The trial was completed by 42 cerebral infarction patients (control group, 12; SA group, 11; rTMS group, 8; SAEM-CS group, 11). All patient groups underwent two sessions of CSRT per day. SA, rTMS, and SAEM-CS were conducted once per day, 5 days per week, for 3 weeks. The primary outcome (motor function recovery) was evaluated using the Fugl-Mayer assessment (FMA). Other scales were used to assess cognitive function, activities of daily living, walking, quality of life, and stroke severity, which were secondary outcomes. Results There were significant changes (week 7–week 0) between groups in the FMA upper extremity (FMAUE), FMA total (FMAT), modified Barthel index (MBI), and functional independent measurement (FIM) scores. There were no significant changes in the scores of other outcome measures. FMAUE ($p=0.015$), FMAT ($p=0.023$), MBI ($p=0.002$), and FIM ($p<0.001$) scores significantly increased in the rTMS group compared with the control group and FMAUE ($p=0.016$), FMAT ($p=0.012$), MBI ($p=0.026$), and FIM ($p=0.012$) scores significantly increased in the rTMS group compared with the SAEM-CS group. However, there were no significant changes in the SA or SAEM-CS group. Conclusions Low-frequency rTMS in the contralesional hemisphere had long-term therapeutic effects on upper extremity motor function recovery and on improvements in activities of daily living. SAEM-CS had no positive synergistic effects of SA and rTMS on motor function recovery, cognitive function, activities of daily living, walking, quality of life, and stroke severity. Trial Registration URL: cris.nih.go.kr. Unique identifier: KCT0001768, retrospectively registered (registration date: January 14, 2016).

Background

Stroke is the second most common cause of death and the leading cause of adult disability worldwide [1]. Cerebral infarction (CI) is a common disease with high mortality, recurrence, and disability rates, which accounts for approximately 70% of strokes [2]. Conventional treatment of stroke patients includes pharmacological treatments, surgery, and multiprofessional rehabilitation. These treatments can promote recovery to some extent; however, no single intervention clearly and definitively contributes to stroke recovery. Therefore, stroke treatment strategies should combine multiple disciplines such as neurology, rehabilitation medicine, and traditional medicine [3,4].

Scalp acupuncture (SA) is a specialized acupuncture technique in which a filiform needle is used to penetrate specific stimulation areas on the scalp [5]. Baihui (GV20)-based SA could improve infarct volume and neurological function scores and exhibit potential neuroprotective roles in experimental ischemic stroke [6]. SA is commonly used during the acute, recovery, and sequelae stages of ischemic and hemorrhagic strokes [7-10].

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method that can change the excitability of the brain cortex for at least several minutes. The nature of the after-effect depends on the frequency, intensity, and pattern of stimulation [11]. Currently, rTMS is being explored as a novel therapy for modulating cortical excitability to improve the motor function of stroke patients [12]. High-frequency rTMS (HF-rTMS; more than 5

Hz) applied to the ipsilesional hemisphere reportedly facilitates cortical excitability [13], whereas low-frequency rTMS (LF-rTMS; 1 Hz or less) applied to the contralesional hemisphere decreases cortical excitability [14-19].

Neural plasticity is the ability of the brain to develop new neuronal connections, acquire new functions, and compensate for impairments. These processes are crucial for motor recovery after stroke [20-22]. Current research aims to determine whether using combinations of various novel stroke rehabilitations can synergistically improve motor recovery [23].

SA and electromagnetic convergence stimulation (SAEM-CS) involves the simultaneous application of SA stimulation of SIAN's MS6 and MS7 at the upper limb regions of the ipsilesional hemisphere and LF-rTMS over the M1 region's hot spot (motor cortex at the contralesional hemisphere) [24]. We compared the efficacies of SAEM-CS, conventional stroke rehabilitation therapy (CSRT), rTMS, and SA for motor-function recovery (primary aim) and cognitive function, activities of daily living, walking, quality of life, and stroke severity (secondary aims) in inpatients with CI to investigate the synergistic effects of SA and rTMS on CI.

Methods

This study followed the standard protocol items of the Recommendations for Interventional Trials (SPIRIT) and CONSORT statement. Detailed methods of this study have been reported previously [24].

Study design

This study was an outcome assessor-blinded single-center randomized controlled pilot clinical trial with a 1:1:1:1 allocation ratio. Participants (n = 60) who fit the inclusion criteria were randomly allocated to the control group (n = 15), SA group (n = 15), rTMS group (n = 15), and SAEM-CS group (n = 15). All groups received CSRT twice per day, five times per week, for a total of 15 times over the course of a 3-week hospitalization period at Chonnam National University Hospital. In addition, the SA group received SA therapy, the rTMS group received rTMS therapy, and the SAEM-CS group received SAEM-CS therapy once per day. Outcome measures were determined at baseline (week 0), 3 weeks after the first intervention (week 3), and 4 weeks after completion of the intervention (week 7). The study design is summarized in Figure 1.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-2015-114). This trial was registered at cris.nih.go.kr (registration number: KCT0001768). All patients provided written informed consent before participating in this study.

Participant recruitment

To achieve adequate participant enrollment to reach the target sample size, all CI patients who finished treatment for early acute stage CI at the Department of Neurology of Chonnam National University Hospital were screened by physical and rehabilitation medicine doctors. Patients who received an explanation regarding this study from the clinical research coordinator and who voluntarily signed a consent form were transferred to the Department of Physical and Rehabilitation Medicine to participate in this study. The clinical research coordinator

continuously monitored the medical conditions of enrolled participants for improved adherence to intervention protocols.

Participation

There were six inclusion criteria: (1) age older than 19 years; (2) incipient CI confirmed by computed tomography or magnetic resonance imaging examination; (3) CI that resulted in motor and sensory disorders within 1 month of study onset; (4) could undergo rehabilitation therapy after hospitalization at the Department of Physical and Rehabilitation Medicine of Chonnam National University Hospital; (5) modified Rankin scale (mRS) score of 2–4; and (6) voluntarily signed an informed consent form.

Subjects whose general condition was not fit for SA and rTMS therapies were excluded. Detailed exclusion criteria were as follows: (1) prior history of brain lesion (e.g., stroke, serious mental illness, loss of consciousness accompanied by head trauma, brain surgery, or seizure disorder); (2) presence of other serious illnesses (e.g., cancer, Alzheimer's disease, epilepsy, head trauma, or cerebral palsy); (3) transient ischemic attack; (4) contraindications to electromagnetic stimulation (e.g., metal implants in the brain, implanted electronic devices in the body such as nondetachable ferromagnetic metals, metal-sensitive implants less than 30 cm away from the brain such as cochlear implants, pacemakers, aneurysm clips or coils, stents, bullet fragments, deep brain stimulation, vagus nerve stimulators, jewelry, or hairpins); (5) continuous convulsion symptoms; (6) previous craniectomy or shunt surgery; (7) increased intracranial pressure symptoms such as headache, vomiting, or nausea; (8) seizure disorder or epilepsy after CI; (9) prior history of stroke accompanied by a clear clinical sign; (10) contraindications to SA (e.g., scalp scarring, inflammation from scalp injury, infection in the treatment region, inability to stop blood flow due to clotting disturbances such as hemophilia, serious unusual response after acupuncture treatment); (11) pregnant or breastfeeding; (12) disagreement with informed consent; and (13) scheduled for surgery within 2 weeks.

Randomization and blinding

After signed informed consent and baseline measurements were obtained, random allocation software (developed by M. Saghaei, MD, Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran) was used to assign a serial number to the 60 research volunteers and to randomly allocate 15 of them to each group. The serial number codes were inserted in sealed opaque envelopes, kept in a double-locked cabinet, and opened in the presence of the patient and a guardian.

We had no choice but to adopt a single outcome assessor blinding approach because sham treatment was impossible due to the characteristics of SA, which included scalp penetration. During the study, the assessor was blinded to group assignments, and data analysts without conflicts of interest were involved in this study.

Implementation

A clinical research coordinator generated the allocation sequence, enroll participants, and assign participants to interventions.

Intervention

All participants underwent conventional stroke rehabilitation therapy (CSRT), which focused on practicing fine and gross motor movements, activities of daily living, task-oriented therapeutic exercises, and muscular electrical stimulation therapy as needed. Training for swallowing and improving language was also performed for dysarthria. These sessions were conducted for 30 minutes (excluding Saturdays and Sundays) twice daily for 3 weeks for a total 15 times. SA, rTMS, and SAEM-CS therapies were conducted once daily for 20 minutes (excluding Saturdays and Sundays) for 3 weeks for a total of 15 times.

SA was conducted as follows: one or two needles were horizontally inserted approximately 3 cm into the lesion site and upper limb regions of MS6 (line connecting GV21 and GB6) and MS7 (line connecting GV20 and GB7) in the directions from GV21 to GB6 and from GV20 to GB7 [10]. Manual stimulation and electroacupuncture were not applied, and the needles (KOS 92 nonmagnetic steel acupuncture needles, size 0.25 mm × 30 mm, product no. A84010.02; Dongbang Acupuncture, Inc., Boryeong, Republic of Korea) were left in position for 20 minutes (Table 1).

The rTMS was conducted as follows: a 70-mm figure-8 coil and a Magstim Rapid stimulator (Magstim Co., Dyfed, UK) were used to deliver 1 Hz of rTMS to the skull of the contralesional hemisphere at the site that elicited the largest motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle of the unaffected upper limb. One LF-rTMS session consisted of 1200 pulses and lasted for 20 minutes. Stimulation intensity was set to 80% of the motor threshold of the FDI muscle, which was defined as the lowest intensity of stimulation that provokes MEPs. All patients sat in a reclining wheelchair and were asked to relax as much as possible with their heads strapped to a headrest [25].

The SAEM-CS was conducted as follows: the aforementioned SA and LF-rTMS therapies were performed simultaneously. After SA treatment of MS6 and MS7 on the lesion side, LF-rTMS stimulation was conducted on the contralateral hemisphere for 20 minutes.

Outcome measurements

The primary outcome was motor function, and the secondary outcomes were cognitive function, activities of daily living, walking, quality of life, and stroke severity. Primary and secondary outcome assessments were conducted at baseline (before intervention), 3 weeks after the first intervention, and 4 weeks after completion of intervention (except Korean Mini Mental State Examination [K-MMSE], American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale [ASHA-NOMS], and functional ambulatory category [FAC]).

The primary outcome was assessed via changes in the Fugl-Mayer assessment (FMA) scale scores for motor function. The FMA scale was developed as the first quantitative evaluation instrument for measuring sensorimotor stroke recovery and included an assessment of the upper extremities (33 items; score range, 0-66) and lower extremities (17 items; score range, 0-34) [26].

Secondary outcome measures were assessed via changes in the National Institutes of Health Stroke Scale (NIHSS) score, modified Barthel index (MBI), functional independent measurement (FIM) score, K-MMSE score, ASHA-NOMS score, FAC, European Quality of Life-5 Dimensions (EQ-5D), modified Ashworth scale (MAS) score, hand grip strength test, MEPs, mRS score, and 9-hole peg test (9HPT).

The NIHSS, which was developed by the United States National Institutes of Health, is a standardized stroke severity scale used to describe the neurological deficits of stroke patients, and it strongly predicts the likelihood of a patient's recovery after stroke [27]. The MBI is a scale that measures 10 basic aspects of daily life activities related to self-care and mobility [28]. The FIM is an assessment of everyday movement performance that evaluates 13 detailed items of motor FIM and five detailed items of cognitive FIM [29]. The MMSE is a brief 30-point questionnaire that is used to screen for cognitive impairment. In this study, we used the K-MMSE [30]. The ASHA-NOMS is a seven-stage dysphagia scale developed by the American Speech-Language-Hearing Association to evaluate the severity of dysphagia [31]. The FAC was designed to evaluate walking ability, which is categorized into six ranks [32]. The EQ-5D is a generic instrument for describing and valuing health-related quality of life [33]. The MAS assesses muscles by measuring spasticity in the wrist and elbow joints while the joints are maximally bent [34]. The hand grip strength test evaluates muscle strength in the hands [16].

In this study, MEPs were evoked by stimulating the primary motor cortex representing hand grip muscles without pain. Then, responses of the FDI muscle were observed. MEPs are useful for predicting functional recovery after CI. The latency and amplitude of the MEP responses were recorded [35]. The mRS is a six-point ordinal hierarchical scale that describes global disability and focuses on mobility [36]. The 9HPT is useful for measuring the dexterity of relatively well-recovered patients [37].

Statistical analyses

Sample size calculation was detailed in our study protocol [24]. We performed per-protocol analysis for the assessment of efficacy and a supplementary full analysis set. Analysis was performed by blinded biostatisticians using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA) using two-sided significance tests with a 5% significance level. Continuous variables were presented as means and standard deviations (SD), and categorical variables were presented as count frequencies and percentages.

Baseline data were collected and compared by first using the independent k-sample Kruskal-Wallis test, nonparametric tests, and χ^2 test. Differences between all outcome value changes (week 0 vs. week 7) in the four groups were compared by the two related samples test and the Wilcoxon signed-rank test (nonparametric tests). Values of FMAUE, FMA lower extremity (FMALE), FMA total, NIHSS, MBI, FIM, 9HPT, AHSA-NOMS, FAC, mRS, EQ-5D, K-MMSE, MAS elbow, and MAS ankle were compared by repeated-measures analysis of variance (ANOVA) across two to three testing time points (week 0, week 3, week 7). An F test was conducted to detect differences between therapies, and the Scheffé post hoc test was conducted to identify groups. Differences between two groups of outcome value changes (week 0 vs. week 7 and week 0 vs. week 3; significant changes were observed in the ANOVA and the Scheffé post hoc test) were compared by the two independent samples test and the Mann-Whitney U test (nonparametric test).

Results

Participants

We recruited participants between July 31, 2015, and December 31, 2017. During the study period, 2200 patients were assessed for eligibility and 2140 were excluded due to nonconformity to the inclusion criteria, conformity to the exclusion criteria, or refusal to participate. Sixty patients were included in this study and were randomly assigned to four groups: control group, 15; SA group, 15; rTMS group, 15; and SAEM-CS group, 15. Three did not

complete treatment in the control group. Two did not complete treatment and two were lost to follow-up in the SA group. One exited the study due to orthopedic surgery, four did not complete treatment, and two were lost to follow-up in the rTMS group. One exited the study due to orthopedic surgery, two did not complete treatment, and one was lost to follow-up in the SAEM-CS group (Fig. 2). The results of the per-protocol analysis for the assessment of efficacy were not different from those of the full analysis set. Data for 42 CI patients were used in the final analysis.

Baseline characteristics

Participants were divided into the control group (n=12), SA group (n=11), rTMS group (n=8), and SAEM-CS group (n=11). Baseline demographic characteristics of the 42 CI patients in the four groups, including sex, age, lesion site, and all variables, are presented in Table 3. No significant differences in the baseline demographic characteristics were detected among the four groups (P<0.05; Table 2).

Efficacy of primary and secondary outcomes

All variables at each testing time point are detailed in Table 4. All variables except ASHA-NOMS, K-MMSE, and FAC were estimated at week 0 (baseline), week 3 (end of intervention), and week 7 (follow-up). ASHA-NOMS, K-MMSE, and FAC were estimated at week 0 (baseline) and week 3 (end of intervention; Table 3).

After 3 weeks of intervention, we observed significant improvements in the control group (changes in the FMALE, FMA total [FMAT], NIHSS, MBI, FIM, 9HPT, and mRS scores; week 0 vs. week 7), SA group (changes in the FMAUE, FMALE, FMAT, NIHSS, MBI, and FIM scores; week 0 vs. week 7), rTMS group (changes in the FMAUE, FMALE, FMAT, NIHSS, MBI, FIM, 9HPT, mRS, and EQ-5D scores; week 0 vs. week 7), and SAEM-CS group (changes in the FMAUE, FMALE, FMAT, MBI, FIM, and mRS scores; week 0 vs. week 7; Table 4).

Repeated-measures ANOVA showed a significant interaction between time and group with respect to FMAUE (F=3.82; p=0.002), FMAT (F=3.15; p=0.008), MBI (F=4.27; p=0.001), FIM (F=3.06; p=0.010), and EQ-5D (F=4.52; p=0.014; Table 5).

Changes in the FMAUE scores (week 0 vs. week 3) of the rTMS group were significantly larger than those of SAEM-CS group, and the changes in the FMAUE scores (week 0 vs. week 7) of rTMS group were significantly larger than those of control and SAEM-CS group according to Scheffé post hoc test (Table 6). Changes in the FMAT scores (week 0 vs. week 7) of the rTMS group were significantly larger than those of control and SAEM-CS group according to Scheffé post hoc test (Table 6).

Changes in the MBI scores (week 0 vs. week 3) of the rTMS group were significantly larger than those of control group, and the changes in the MBI scores (week 0 vs. week 7) of the rTMS group were significantly larger than those of the control and SA groups according to Scheffé post hoc test (Table 6).Changes in the FIM scores (week 0 vs. week 7) of the rTMS group were significantly larger than those of the control and SA groups according to Scheffé post hoc test (Table 6).

We conducted multiple comparisons of FMAUE, FMAT, MBI, and FIM, and significant score changes (week 0 vs. week 3 and week 0 vs. week 7) were observed in the ANOVA and Scheffé post hoc test for the four groups to investigate the synergistic effects of SA and rTMS.

Changes in the MBI (p=0.005) and FIM (p=0.03) (week 0 vs. week 3) scores of the rTMS group were significantly larger than those of control group. Changes in FMAUE (p=0.026) and MBI (p=0.043) (week 0 vs. week 3) scores of the rTMS group were significantly larger than those of SAEM-CS group (Table 7).

Changes in FMAUE(p=0.015), FMAT (p=0.023), MBI (p=0.002), and FIM (p<0.001) scores (week 0 vs. week 7) of the rTMS group were significantly larger than those of the control group. Changes in FMAUE (p=.016), FMAT (p=0.012), MBI (p=0.026), and FIM (p=0.012) scores (week 0 vs. week 7) of the rTMS group were also significantly larger than those of the SAEM-CS group. Changes in MBI (p=0.016) and FIM (p=0.008) scores (week 0 vs. week 7) of the rTMS group were significantly larger than those of the SA group (Table 8).

Safety evaluation

Adverse events that occurred in this study were recorded on a case report form after evaluating their relationships with the intervention. Fortunately, no adverse events that were related to the intervention occurred in this study.

Discussion

To our knowledge, this is the first randomized controlled study to investigate the synergistic effects of SA and rTMS on motor-function recovery, stroke severity, activities of daily living, cognitive function, dysphagia, walking ability, quality of life, and spasticity of CI patients by comparing the effects of simultaneous application of LF-rTMS and SA with the effects of SA, LF-rTMS, CSRT. There were several main findings. First, rTMS combined with CSRT led to better improvements in FMA, MBI, and FIM than CSRT alone and SAEM-CS combined with CSRT. Second, SA combined with CSRT and SAEM-CS combined with CSRT did not lead to significant differences compared with CSRT alone. Third, SAEM-CS did not show the positive synergistic effects of SA and rTMS on motor-function recovery, stroke severity, activities of daily living, cognitive function, dysphagia, walking ability, quality of life, and spasticity of CI patients.

Effect of CSRT on patients with CI

CSRT itself has some beneficial effects on motor recovery, activities of daily life, and stroke severity. These results may be related to the therapeutic effects of physical therapy, occupational therapy, and functional electrical stimulation. Two systematic reviews have suggested that the intensity of stroke rehabilitation is an important factor associated with better and faster improvement [38,39]. Intensive occupational therapy was confirmed to be significantly beneficial in a study involving a large number of patients with upper limb hemiparesis after stroke [40].

Analysis of the efficacy of SA for patients with CI

SA combined with CSRT has a beneficial effects on motor-function recovery, stroke severity, and activities of daily living of CI patients, however, there were no significant differences in primary and secondary outcome score changes between the SA group and control group. These results may be related to acupoint specificity, acupuncture manipulation, and electrical stimulation.

Acupuncture is a complex intervention involving both specific and nonspecific factors associated with therapeutic benefits. Apart from needle insertion, issues such as needling sensation, psychological factors,

acupoint specificity, acupuncture manipulation, and needle duration also have relevant influences on the therapeutic effects of acupuncture [41].

The selection and compatibility of acupoints are considered to have a direct effect on the therapeutic effects. According to the concept of “holism” in Traditional Chinese Medicine, acupoints in limbs, especially those located below the elbow and knee joints, are very important for managing organ and meridian diseases. These points can be therapeutic for local problems and for the whole body [42]. A systematic review of reports of acupuncture treatment for CI revealed 24 studies that used both SA and body acupuncture, 28 studies that used body acupuncture, and 4 studies that used only SA [43]. Both SA and body acupuncture were used during clinical trials that reported positive effects of acupuncture for ischemic stroke [44,45].

When SA was used to treat stroke patients, manipulation or electroacupuncture (acupuncture combined with electrical stimulation) were usually used to reinforce the therapeutic effects of SA. There are some methods of reinforcing-reducing acupuncture manipulations in Traditional Chinese Medicine. In clinical practice, mastering the reinforcing-reducing manipulations of acupuncture will contribute to improvements in therapeutic effects [46]. With various factors of manipulation, including lifting-thrusting, twirling-rotating, and variations in the direction, angle, and depth of needle insertion, it is possible to affect the outcomes of acupuncture treatment [47,48]. In most systematic reviews reporting acupuncture for neurogenesis with experimental ischemic stroke [49], Baihui (GV20)-based SA for experimental ischemic stroke [6], and SA for stroke recovery in randomized controlled trials [10], electroacupuncture or manipulation of twirling (needles should be twirled more than 200 times per minute) was applied.

This study aimed to investigate the synergistic effects of SA and rTMS on stroke. Therefore, the same acupuncture treatment method used for the SAEM-CS approach must be used for SA therapy. Subsequently, we could not use the combination of SA and body acupuncture, manipulation, and electroacupuncture to reinforce the therapeutic effects of SA in the SA group.

Analysis of the efficacy of LF-rTMS for patients with CI

LF-rTMS combined with CSRT has beneficial effects on motor-function recovery, stroke severity, activities of daily living, walking ability, and quality of life of CI patients. The rTMS group showed better effects on motor-function recovery and activities of daily living than the control group and SAEM-CS group at 4 weeks after the intervention, however, there were no significant differences in outcome score changes except for MBI and FIM (week 0 vs. week 3) between the rTMS group and control group. These results are similar to those of a previous study [17] and may be related to the long-term effects of rTMS on stroke.

LF-rTMS can inhibit cortical excitability in the stimulated hemisphere, facilitate excitatory interhemispheric balance, increase contralesional hemisphere excitability, and decrease interhemispheric inhibition to promote the recovery of motor function [50]. Several clinical trials have reported no significant effects of LF-rTMS on upper limb motor-function recovery [51-53]. However, other studies have confirmed that rTMS produces significant long-term effects that promote the functional reconstruction of the brain neural network and plays a lasting regulatory role in modulating cortical excitability at the stimulation site and remote areas [54-56]. Long-term effects are more important than short-term effects because long-lasting beneficial effects of rTMS on upper limb motor function are more reliable indicators of successful clinical intervention. Our results showed that LF-rTMS had

long-lasting therapeutic effects on upper limb motor-function recovery and activities of daily living for patients with CI.

Analysis of the efficacy of SAEM-CS for patients with CI

SAEM-CS is a treatment technique that combines LF-rTMS over the M1 region hot spot (motor cortex at the contralesional hemisphere) and SA stimulation of MS6 and MS7 at the upper limb regions of the ipsilesional hemisphere to promote optimal functioning in stroke patients. rTMS creates a powerful magnetic field near the stimulated area; therefore, all metal materials must be removed from the patient [57]. For rTMS and SA therapies that are conducted simultaneously (during SAEM-CS), we use a KOS92 nonmagnetic steel acupuncture needle that contains much higher nitrogen than STS304N1; therefore, even with high processing volumes, the needle has no magnetic properties [24].

SAEM-CS combined with CSRT has beneficial effects on motor-function recovery and activities of daily living of CI patients. However, there were no significant differences in primary and secondary outcome score changes between the SAEM-CS group and control group. Changes in FMAUE, FMAT, MBI, and FIM scores of the SAEM-CS group were significantly smaller than those of the rTMS group. These results showed that SAEM-CS does not have the positive synergistic effects of SA and rTMS and that simultaneously applied SA reduces the long-term effects of rTMS on motor-function recovery. This may be related to homeostatic metaplasticity.

When stroke neurorehabilitation therapies are combined, Hebbian plasticity and homeostatic metaplasticity must be considered. Hebbian plasticity reinforces the neural connections between paretic muscles and the residual motor area. Homeostatic metaplasticity, which stabilizes the activity of neurons and neural circuits, can either augment or reduce the synergistic effects, depending on the timing of combination therapy and types of neurorehabilitation that are used. Inappropriate interventions and timing of combinations may eliminate the synergistic effects due to homeostatic metaplasticity [23].

Several studies of combined neurorehabilitation therapies have not shown positive synergistic effects on stroke due to homeostatic metaplasticity. A few studies have reported no synergistic effects after combining priming HF-rTMS [58] and LF-rTMS [59] with stroke neurorehabilitation. Simultaneous combinations of neurorehabilitation approaches are not always synergistically effective for motor recovery in stroke patients. Hesse et al. studied the use of simultaneous transcranial direct current stimulation (tDCS) and robot-assisted arm training for subacute stroke patients with severe motor function deficits and found that neither inhibitory tDCS over the contralesional M1 nor excitatory tDCS over the ipsilesional M1 enhanced the effects of robot-assisted arm training when compared with robot-assisted training alone [60].

The effects of combination therapies depend not only on the timing, type, session, and intensity of the intervention but also on the severity of motor function, sex, pathology, genetic factor, phase, and lesion site after stroke, possibly due to the heterogeneous neural reorganization response to stroke [23].There could be several reasons that SAEM-CS did not show the positive synergistic effects of SA and rTMS in our study. First, SA and LF-rTMS may have different therapeutic mechanisms in stroke; therefore, SA reduced the long-term effects of LF-rTMS. Bilateral stimulation may reduce synergistic effects due to homeostatic metaplasticity. Ragertet al. reported that preconditioning right M1 with 1-Hz rTMS significantly decreased the excitability-enhancing effects of subsequent left M1 iTBS on RCs. Application of 1-Hz rTMS over the right M1 alone and iTBS over the left M1 alone increased RC in the left M1 relative to sham interventions for healthy subjects [61]. Second, it can be

caused by simultaneous timing. Nitscheet et al. demonstrated that homeostatic plasticity occurred when both excitability-changing protocols were applied simultaneously. Homeostatic plasticity might work to maintain the global network function within the normal physiological range, thereby nullifying the effects of both affected rTMS and unaffected rTMS [62]. A recent study indicated that the order of bilateral hemisphere stimulation was important for synergic effect, suggesting that bilateral stimulation in stroke patients is less influenced by homeostatic metaplasticity. Wang et al. used a priming protocol to apply inhibitory 1-Hz rTMS to the contralesional M1 and subsequent excitatory iTBS to the ipsilesional M1 and also performed the reverse, followed by conventional rehabilitation for stroke patients. The first combination resulted in better improvement in hand function than the second combination [63]. Third, in our study, we selected patients hospitalized within 1 month after acute stroke to increase the homogeneity of the experiment population. Two studies have reported that noninvasive brain stimulation might have no effect on motor recovery for some acute phase stroke patients [51,64]. Zhang et al. reported that subjects of most studies investigating the efficacy of LF-rTMS for stroke-induced upper limb motor deficits had chronic subacute stroke [65].

Limitations

This study had some limitations. First, our trial was a pilot study with a small sample size. We lost some subjects because of various reasons; therefore, the number of subjects included in the final analysis was small. Second, according to our study design, we did not perform outcome measurements of K-MMSE, ASHA-NOMS, or FAC at week 7. Therefore, we did not explore the long-term additional effects on cognitive function, dysphagia, and walking. Third, our study lacked long-term follow-up and evaluation. Although we conducted 3 weeks of treatment and 4 weeks of follow-up, this was not sufficient to assess the long-term efficacy of SA, rTMS, and SAEM-CS. Fourth, we did not investigate synergistic effects of SA and rTMS through various combination methods. We used only simultaneous application of SA at the ipsilesional hemisphere and LF-rTMS over the contralesional hemisphere in combination with SA and rTMS. Further studies of an effective combination of SA and rTMS (i.e., LF rTMS-primed SA or SA-primed LF-rTMS or HF rTMS-primed SA or SA-primed HF-rTMS) should be performed. Fifth, many previous studies exploring the effects of rTMS and SA on motor-function recovery after stroke have focused on subacute and chronic stroke patients. However, our study included only patients with acute CI, not patients with subacute and chronic CI.

Conclusions

Many previous studies have suggested that SA and rTMS were effective treatment methods for stroke. We thought that simultaneous application of SA and rTMS might show positive synergistic effects. However, our findings were different from what we expected.

Several conclusions can be drawn from the results of our study. First, LF-rTMS over the contralesional hemisphere had long-term therapeutic effects on upper extremity motor-function recovery and on improving activities of daily living. Second, simultaneous application of SA and LF-rTMS did not have the positive synergistic effects of SA and rTMS on motor-function recovery, cognitive function, activities of daily living, walking, quality of life, and stroke severity. Third, SA may reduce long-term effects of LF-rTMS on motor-function recovery and activities of daily living.

We think the results of our study investigating the synergistic effects of SA and rTMS on motor-function recovery of patients with stroke may vary greatly depending on the subject characteristics (time after stroke, level of severity, site, and size of lesion), parameters of rTMS and SA administration, and timing of the combination. Therefore, it is difficult to conclude that there were no positive synergistic effects of SA and rTMS.

Further studies should investigate the influence of interindividual characteristics on the response to SA and rTMS and the mechanisms of action of each approach. These results are essential for guiding the development of these combined treatment approaches.

Abbreviations

ADL, activities of daily living; ASHA-NOMS, American Speech-Language-Hearing Association National Outcome Measurement System Swallowing Scale; CI, cerebral infarction; CSRT, conventional stroke rehabilitation therapy; EQ-5D, European Quality of Life-5 Dimensions; FAC, Functional Ambulatory Category; FIM, Functional Independent Measurement; FMA, Fugl–Mayer Assessment; FMALE, Fugl–Mayer Assessment Low Extremity; FMAT, Fugl–Mayer Assessment Total; FMAUE, Fugl–Mayer Assessment Upper Extremity; HF rTMS, High frequency repetitive transcranial magnetic stimulation; LF rTMS, Low frequency repetitive transcranial magnetic stimulation; MAS, Modified Ashworth Scale; MBI, Modified Barthel Index; MEP, motor evoked potential; MMSE, Mini Mental State Examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; 9HPT, 9-hole peg test; rTMS, repetitive transcranial magnetic stimulation; SA, scalp acupuncture; SAEM-CS, scalp acupuncture and electromagnetic convergence stimulation

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-2015-114). This trial was registered at cris.nih.go.kr (registration number: KCT0001768). The purpose and potential risks of this clinical trial will be fully explained to the participants and their families. All patients were asked to provide written informed consent before participating in this study.

Consent for publication

Written informed consent for publication of individual details and accompanying images will be obtained from the trial participants. The consent form is in possession of the authors and available for review by the Editor-in-Chief.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflicts of interest concerning this article.

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Authors' Contributions

Han JY and Kim JH designed or conceptualized the trial, wrote the initial draft, and analyzed data. Song MK and Park GC designed the trial and conducted the trial. Lee JS is responsible for planning data analysis and interpreting the data resulting from the trial. All authors read, revised the manuscript and approved the final manuscript.

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Tables

Table 1. Revised Standards for Reporting Intervention in Clinical Trials of Acupuncture (STRICTA)

	Item Criteria	Description
1.Acupuncture rationale	1a) Style of acupuncture	Korean Medicine Therapy
	1b) Reasoning for treatment provided – based on historical context, literature sources, and/or consensus methods, with references where appropriate	1) Discussion among four doctors that practice Korean medicine (consensus) 2) Textbook of acupuncture and moxibustion medicine 3) Relevant articles Selection of treatment regions based on textbooks, related papers, and expert discussions
	1c) Extent to which treatment varied	Standardized treatment
2. Details of needling	2a) Number of needle insertions per subject per session (mean and range where relevant)	2−4
	2b) Names (or location if no standard name) of points used (uni-/bilateral)	SIAN's MS6; MS7 of the lesional hemisphere
	2c) Depth of insertion, based on a specified unit of measurement or on a particular tissue level	Needles were horizontally inserted into the subcutaneous tissue of the scalp, about 3 cm deep.
	2d) Responses sought	No de qi or muscle twitching – only sensation due to needle insertion
	2e) Needle stimulation	None
	2f) Needle retention time	20-min per session
	2g) Needle type	KOS92 nonmagnetic steel disposable needles (0.25-mm diameter and 30-mm long), manufactured by Dong Bang Acupuncture, Inc.
3. Treatment regimen	3a) Number of treatment sessions	15
	3b) Frequency and duration of treatment sessions	Five times/week for 3 weeks, 20-min per session
4. Other treatment components	4a) Details of other interventions administered to the acupuncture group	Conventional stroke rehabilitation therapy
	4b) Setting and context of treatment – including instructions to practitioners – as well as information and explanations given to patients	Practitioner-patient conversation about the context of the treatment, life habits, and daily life management
5. Practitioner background	5a) Description of participating acupuncturists	Korean medicine doctor with the following qualifications: 6 years of formal university training in Korean medicine, a license, and at least 2 years of clinical experience
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify the choice	Wang Y, Shen J, Wang XM, Fu DL, Chen CY, Lu LY et al. Scalp Acupuncture for Acute Ischemic Stroke: A Meta-Analysis of Randomized Controlled Trials. Evid Based Complement Altern Med 2012;2012:480950.: Lee SJ, Shin BC, Lee MS, Han CH, Kim JI. Scalp acupuncture for stroke recovery: A systematic review and meta-analysis of randomized controlled trials. European J Integr Med. 2013;5:87-99
	6b) Precise description of	Conventional stroke rehabilitation therapy for control, rTMS, and

	the control or comparator; details for items 1−3 above with the use of sham acupuncture or any other type of acupuncture-like control	SAEM-CS groups. LF-rTMS applied to the hot spot of the M1 region (the motor cortex at the contralesional hemisphere) for the rTMS group and LF-rTMS applied to the same M1 and simultaneous SA stimulation over the upper MS6 and MS7 region of the lesional hemisphere for the SAEM-CS group.

Table 2 Homogeneity of the Demographic Characteristics for 4 Groups

Dependent Variables	Control group (n=12) Mean(SD) or n(%)	SA group (n=11) Mean(SD) or n(%)	rTMS group (n=8) Mean(SD) or n(%)	SAEM-CS group (n=11) Mean(SD) or n(%)	*F or x²(P)*
Age (y)	62.17(16.25)	64.45(14.75)	67.00(12.92)	67.55(12.53)	84.69(.458)*
Gender (Male)	7(58.3%)	7(63.6%)	5(62.5%)	4(36.4%)	2.11(.550)*
Hemiparesis (Lt)	8(66.7%)	5(45.5%)	5(62.50%)	7(63.67%)	1.26(.738)*
FMA Upper Extremity	44.42(26.57)	26.18(29.20)	33.13(19.40)	42.64(27.21)	1.163(.337) †
FMA Lower Extremity	19.33(11.22)	19.27(8.97)	19.63(8.77)	19.45(12.89)	0.01(1.000) †
FMA Total	63.75(36.00)	45.45(36.05)	52.75(25.02)	62.09(39.03)	0.66(.584) †
NIHSS	3.50(4.46)	5.73(3.77)	5.13(3.23)	4.18(4.77)	0.62(.604) †
MBI	65.58(18.92)	55.36(23.08)	41.63(22.60)	57.55(30.27)	1.60(.205) †
FIM	93.83(16.72)	87.36(21.46)	75.38(13.20)	85.73(35.99)	0.96(.423) †
9HPT	93.65(39.18)	89.43(42.73)	108.75(31.83)	81.90(42.01)	0.73(.538) †
AHSA-NOMS	6.83(0.58)	6.45(0.93)	5.38(1.92)	6.45(0.82)	3.00(.043) †
FAC,	2.08(1.83)	1.18(1.78)	1.38(1.51)	1.73(1.68)	0.60(.622) †
mRS	3.08(0.90)	3.45(0.69)	3.63(0.52)	3.27(0.79)	0.95(.425) †
EQ-5D	9.75(2.73)	9.73(3.41)	12.13(1.64)	10.09(3.27)	1.34(.275) †
K-MMSE	26.42(3.75)	25.00(4.56)	26.13(3.52)	23.00(4.29)	1.56(.216) †
MAS Elbow	0.08(0.29)	0.45(0.93)	0.13(0.35)	0.27(0.47)	0.92(.442) †
MAS Ankle	0.25(0.62)	0.36(0.67)	0.00(0.00)	0.36(0.50)	0.87(.466) †
Griptest Dominant hand	31.17(18.15)	27.91(9.68)	25.63(13.74)	20.55(9.72)	1.26(.302) †
Griptest NonDominant - hand	13.50(15.56)	10.91(16.18)	6.50(9.35)	10.64(10.27)	0.43(.733) †
APBrecording Cortical stim latency	11.83(12.43)	8.31(11.56)	9.45(13.12)	12.33(11.86)	0.27(.848) †
APBrecording Cortical stim Amplitude	258.33(412.71)	372.73(567.00)	188.00(449.58)	576.73(781.20)	0.89(.458) †
AHrecording Cortical stim latency	22.68(22.58)	23.47(22.63)	20.53(24.30)	14.52(20.20)	0.37(.778) †
AHrecording Cortical stim Amplitude	294.50(471.46)	144.09(181.25)	201.63(353.65)	238.55(362.56)	0.35(.791) †

* P values were determined by $\chi 2$ test

† P values were determined by Tests for Several Independent Samples: Kruskal-Wallis Test

Table 3. Variables at each testing time point

Dependent Variables	Group(N)	Week 0 (Mean±SD)	Week 3 (Mean±SD)	Week 7 (Mean±SD)
FMA Upper Extremity	CG(n=12)	44.42±26.57	49.58±24.33	50.25±23.64
	SAG(n=11)	26.18±29.20	35.27±24.41	39.36±25.24
	rTMSG(n=8)	33.13±19.40	50.13±10.78	56.50±9.70
	SAEM-CSG(n=11)	42.64±27.21	44.91±27.72	47.64±25.32
FMA Lower Extremity	Control group (n=12)	19.33±11.22	24.50±10.41	24.67±10.19
	SAG(n=11)	19.27±8.97	25.27±10.11	24.55±10.53
	rTMSG(n=8)	19.63±8.77	24.50±5.86	28.25±6.78
	SAEM-CSG(n=11)	19.45±12.89	23.64±11.24	25.36±10.57
FMA Total	CG(n=12)	63.75±36.00	74.08±33.22	74.92±31.13
	SAG(n=11)	45.45±36.05	60.55±32.15	63.91±35.02
	rTMSG(n=8)	52.75±25.02	74.63±15.22	84.88±14.24
	SAEM-CSG(n=11)	62.09±39.03	68.55±38.39	73.00±35.56
NIHSS	CG(n=12)	3.50±4.46	3.33±4.03	2.00±2.70
	SAG(n=11)	5.73±3.77	3.09±3.91	3.36±4.08
	rTMSG(n=8)	5.13±3.23	2.88±2.36	2.00±1.85
	SAEM-CSG(n=11)	4.18±4.77	4.00±4.02	3.64±4.48
MBI	CG(n=12)	65.58±18.92	72.42±23.19	81.50±18.53
	SAG(n=11)	55.36±23.08	69.73±29.07	74.00±29.36
	rTMSG(n=8)	41.63±22.60	67.38±19.94	85.13±11.68
	SAEM-CSG(n=11)	57.55±30.27	73.09±25.99	80.55±27.19
FIM	CG(n=12)	93.83±16.72	101.00±20.53	107.33±17.52
	SAG(n=11)	87.36±21.46	98.00±23.23	102.45±23.70
	rTMSG±n=8)	75.38±13.20	97.75±14.74	111.50±8.49
	SAEM-CSG(n=11)	85.73±35.99	101.64±22.55	107.91±23.36
9HPT	CG(n=12)	93.65±39.18	66.59±35.87	58.72±38.28
	SAG(n=11)	89.43±42.73	87.59±45.37	88.94±43.88
	rTMSG(n=8)	108.75±31.83	83.30±40.88	68.56±37.29
	SAEM-CSG(n=11)	81.90±42.01	63.19±39.08	64.56±45.76
AHSA-NOMS	CG(n=12)	6.83±0.58	7.00±0.00	-
	SAG(n=11)	6.45±0.93	6.73±0.65	-
	rTMSG(n=8)	5.38±1.92	6.50±0.76	-

	SAEM-CSG(n=11)	6.45±0.82	6.64±0.92	-
FAC	CG(n=12)	2.08±1.83	2.50±2.07	-
	SAG(n=11)	1.18±1.78	2.64±2.06	-
	rTMSG(n=8)	1.38±1.51	2.63±1.60	-
	SAEM-CSG(n=11)	1.73±1.68	2.73±2.01	-
mRS	CG(n=12)	3.08±0.90	3.08±1.44	2.50±1.45
	SAG(n=11)	3.45±0.69	3.18±1.60	2.80±1.48
	rTMSG(n=8)	3.63±0.52	2.88±1.36	2.63±1.06
	SAEM-CSG(n=11)	3.27±0.79	3.09±1.30	2.55±1.63
EQ-5D	CG(n=12)	9.75±2.73	9.25±2.14	9.08±2.97
	SAG(n=11)	9.73±3.41	10.00±2.14	10.55±2.46
	rTMSG(n=8)	12.13±1.64	10.00±2.45	9.13±1.25
	SAEM-CSG(n=11)	10.09±3.27	9.00±3.13	9.45±3.70
K-MMSE	CG(n=12)	26.42±3.75	26.42±3.48	-
	SAG(n=11)	25.00±4.56	24.91±5.75	-
	rTMSG(n=8)	26.13±3.52	26.50±3.7	-
	SAEM-CSG(n=11)	23.00±4.29	25.09±3.33	-
MAS Elbow	CG(n=12)	0.08±0.29	0.17±0.39	0.17±0.39
	SAG(n=11)	0.45±0.93	0.55±0.69	0.36±0.50
	rTMSG(n=8)	0.13±0.35	0.63±0.52	0.75±0.71
	SAEM-CSG(n=11)	0.27±0.47	0.45±0.82	0.18±0.40
MAS Ankle	CG(n=12)	0.25±0.62	0.33±0.65	0.25±0.62
	SAG(n=11)	0.36±0.67	0.27±0.47	0.36±0.50
	rTMSG(n=8)	0.00±0.00	0.50±0.54	0.38±0.52
	SAEM-CSG(n=11)	0.36±0.50	0.55±0.82	0.27±0.65
Griptest Dominant hand	CG(n=12)	31.17±18.15	28.92±14.32	29.50±13.28
	SAG(n=11)	27.91±9.68	32.55±18.45	29.36±13.17
	rTMSGn=8)	25.63±13.74	28.38±11.62	27.38±9.77
	SAEM-CSG(n=11)	20.55±9.72	21.73±7.77	21.45±9.40
Griptest NonDominant hand	CG(n=12)	13.50±15.56	15.00±12.66	18.42±13.39
	SAG(n=11)	10.91±16.18	11.36±17.18	11.45±17.01
	rTMSG(n=8)	6.50±9.35	9.88±7.90	7.88±5.41
	SAEM-CSG(n=11)	10.64±10.27	11.45±10.83	12.45±11.20
APBrecording Cortical	CG(n=12)	11.83±12.43	9.91±12.31	9.89±12.34
stim latency	SAG(n=11)	8.31±11.56	10.48±12.08	10.37±11.95
	rTMSG(n=8)	9.45±13.12	14.79±12.35	18.29±11.44
	SAEM-CSG(n=11)	12.33±11.86	14.70±11.73	16.83±10.89

APBrecording Cortical stim Amplitude	CG(n=12)	258.33±412.71	409.67±675.5	273.33±435.64
	SAG(n=11)	372.73±567.00	407.64±615.19	492.82±843.53
	rTMSG(n=8)	188.00±449.58	297.75±459.71	441.75±416.07
	SAEM-CSG(n=11)	576.73±781.20	266.00±241.09	882.45±949.47
AHrecording Cortical stim latency	CG(n=12)	22.68±22.58	25.94±23.05	22.03±23.08
	SAG(n=11)	23.47±22.63	23.45±22.76	23.87±23.07
	rTMSG(n=8)	20.53±24.30	15.91±22.13	28.36±24.11
	SAEM-CSG(n=11)	14.52±20.20	15.05±20.93	15.23±21.21
AHrecording Cortical stim Amplitude	CG(n=12)	294.50±471.46	353.08±586.75	255.42±338.39
	SAG(n=11)	144.09±181.25	150.18±216.32	255.45±376.84
	rTMSG(n=8)	201.63±353.65	90.88±143.49	98.50±102.30
	SAEM-CSG(n=11)	238.55±362.56	156.91±265.20	264.91±413.43

CG, control group; SAG, SA group; rTMSG, rTMS group; SAEM-CSG, SAEM-CS group

Table 4 Comparisons (Baseline (week 0) vs. follow-up (week 7) among the 4 Groups

Groups	Dependent Variables	Week 0 (Mean±SD)	Week 7 (Mean±SD)	Difference	*Z*	*p*
CG (n=12)	FMAUE	44.42±26.57	50.25±23.64	5.83±11.30	-1.718	.086
	FMALE	19.33±11.22	24.67±10.19	5.33±6.04	-2.143	.032
	FMAT	63.75±36.00	74.92±31.13	11.17±13.07	-2.225	.026
	NIHSS	3.50±4.46	2.00±2.70	-1.50±2.36	-1.969	.049
	MBI	65.58±18.92	81.50±18.53	15.92±11.94	-2.934	.003
	FIM	93.83±16.67	107.33±17.52	13.50±11.44	-2.599	.009
	9HPT	93.65±39.18	58.72±38.28	-34.93±37.61	-2.666	.008
	AHSA-NOMS	-	-	-	-	-
	FAC	-	-	-	-	-
	mRS	3.08±0.90	2.50±1.15	-0.58±1.07	-2.701	.007
	EQ-5D	9.75±2.73	9.08±2.97	9.67±2.61	-1.168	.243
	K-MMSE	-	-	-	-	-
	MAS Elbow	0.08±0.29	0.17±0.39	0.08±0.52	-0.577	.564
	MAS Ankle	0.25±0.62	0.25±0.62	0.00±0.43	0.000	1.000
	Griptest Dominant hand	31.17±18.15	29.50±13.28	-1.67±7.11	-0.945	.345
	Griptest NonDominant -hand	13.50±15.56	18.42±13.39	4.92±16.23	-0.534	.594
	APBrecording Cortical stim latency	11.83±12.43	9.89±12.34	-1.94±7.16	-0.135	.893
	APBrecording Cortical Stim Amplitude	258.33±412.71	273.33±435.64	15.00±252.14	-0.314	.753
	AHrecording Cortical stim latenc	22.68±22.58	22.03±23.08	0.65±2.31	-0.848	.396
	AHrecording Cortical stim Amplitude	294.50±471.46	255.42±338.39	-39.08±325.71	-0.507	.612
SAG (n=11)	FMAUE	26.18±29.20	39.36±25.24	13.18±15.72	-2.524	.012
	FMALE	19.27±8.97	24.55±10.53	5.27±4.01	-2.549	.011
	FMAT	45.45±36.04	63.91±35.02	18.45±17.01	-2.666	.008
	NIHSS	5.73±3.77	3.36±4.08	-2.36±2.46	-2.615	.009
	MBI	55.36±23.08	74.00±29.36	18.64±18.21	-2.405	.016
	FIM	87.36±21.46	102.45±23.69	15.09±15.12	-2.402	.016
	9HPT	89.43±42.73	88.94±43.88	-0.48±3.76	0.730	.465
	AHSA-NOMS					
	FAC					
	mRS	3.45±0.69	2.80±1.48	-0.65±1.70	-1.552	.121
	EQ-5D	9.73±3.41	10.55±2.46	11.45±2.42	0.423	.673
	K-MMSE					
	MAS Elbow	0.45±0.93	0.36±0.50	-0.09±0.70	-0.447	.655
	MAS Ankle	0.36±0.67	0.36±0.50	0.00±0.77	0.000	1.000
	Griptest Dominant hand	27.91±9.68	29.36±13.17	1.45±6.58	-0.612	.540
	Griptest NonDominant -hand	10.91±16.18	11.45±17.01	0.55±4.25	-0.315	.752
	APBrecording Cortical	8.31±11.56	10.37±11.95	2.064±6.91	-0.730	.465

	stim latency					
	APBrecording Cortical stim Amplitude	372.73±567.00	492.82±843.53	120.09±630.49	-0.674	.500
	AHrecording Cortical stim latenc	23.47±22.63	23.87±23.07	0.40±20.92	-0.676	.499
	AHrecording Cortical stim Amplitude	144.09±181.25	255.45±376.84	111.36±266.37	-1.352	.176
rTMSG (n=8)	FMAUE	33.13±19.40	56.60±9.70	23.38±14.70	-2.524	.012
	FMALE	19.63±8.77	28.25±6.78	8.63±5.24	-2.527	.012
	FMAT	52.75±25.02	84.88±14.24	32.13±17.28	-2.521	.012
	NIHSS	5.13±3.23	2.00±1.85	-3.13±1.27	-2.585	.010
	MBI	41.63±22.60	85.13±11.68	43.50±16.64	-2.521	.012
	FIM	75.38±13.20	111.50±8.49	36.13±6.88	-2.524	.012
	9HPT	108.75±31.83	68.56±37.29	-40.19±35.61	-2.201	.028
	AHSA-NOMS					
	FAC					
	mRS	3.63±0.52	2.75±1.04	-0.88±0.93	-2.333	.020
	EQ-5D	12.13±1.64	9.13±1.25	10.13±1.46	-2.549	.011
	K-MMSE					
	MAS Elbow	0.13±0.35	0.75±0.71	0.38±0.52	-1.890	.059
	MAS Ankle	0.00±0.00	0.38±0.52	0.63±0.74	-1.732	.083
	Griptest Dominant -hand	25.63±13.74	27.38±9.77	1.75±7.19	-0.772	.440
	Griptest NonDominant -hand	6.50±9.35	7.88±5.41	1.38±7.50	-0.631	.528
	APBrecording Cortical stim latency	9.45±13.12	18.29±11.44	8.84±12.66	-1.572	.116
	APBrecording Cortical stim Amplitude	188.00±449.58	441.75±416.07	253.75±573.24	-1.153	.249
	AHrecording Cortical stim latenc	20.53±24.30	28.36±24.11	7.84±20.38	-0.405	.686
	AHrecording Cortical stim Amplitude	201.63±353.65	98.50±102.30	-103.13±305.58	-0.405	.686
SAEM-CSG (n=11)	FMAUE	42.64±27.22	47.64±25.32	5.00±6.70	-2.374	.018
	FMALE	19.45±12.89	25.36±10.57	5.91±6.50	-2.521	.012
	FMAT	62.09±39.01	73.00±35.56	10.91±12.43	-2.601	.009
	NIHSS	4.18±4.77	3.64±4.48	-0.55±1.92	-1.131	.258
	MBI	57.55±30.27	80.55±27.19	23.00±16.12	-2.803	.005
	FIM	85.73±35.99	107.00±19.35	22.18±20.84	-2.805	.005
	9HPT	81.90± 42.01	64.56± 45.76	-17.34±51.43	-1.400	.161
	AHSA-NOMS					
	FAC					

mRS	3.27±0.79	2.55±1.64	-0.91±1.14	-2.271	.023
EQ-5D	10.09± 3.27	9.45± 3.70	10.18± 3.19	-1.119	.263
K-MMSE					
MAS Elbow	0.27± 0.47	0.18± 0.40	-0.09±0.30	-1.000	.317
MAS Ankle	0.36± 0.50	0.27± 0.65	-0.09±0.54	-0.577	.564
Griptest Dominant -hand	20.55± 9.72	21.45± 9.40	0.91± 5.94	-0.670	.503
Griptest NonDominant -hand	10.64± 10.27	12.45± 11.20	1.82± 5.86	-1.014	.310
APBrecording Cortical stim latency	12.33± 11.86	16.83± 10.89	4.50± 10.16	-0.841	.400
APBrecording Cortical stim Amplitude	576.73± 781.20	882.45± 949.47	305.73± 442.54	-1.680	.093
AHrecording Cortical stim latenc	14.52± 20.20	15.23± 21.21	0.71± 1.25	-1.826	.068
AHrecording Cortical stim Amplitude	238.55± 362.56	264.91± 413.43	26.36± 279.46	-0.730	.465

CG, control group; SAG, SA group; rTMSG, rTMS group; SAEM-CSG, SAEM-CS group; FMAUE, FMA Upper Extremity; FMALE, FMA Lower Extremity; FMAT, FMA Total

Difference: Change in value baseline (week 0) vs follow-up (week 7) .

P values were determined by Wilcoxon signed-rank test.

Table 5 Results of repeated measures ANOVA for outcome

Dependent Variables	Source of Variation	SS	df	Mean Square	F	*p*	Significant
FMA Upper Extremity	Time	3043.44	2	1521.72	31.91	.000	S
	Group*Time	1092.10	6	182.02	3.82	.002	S
FMA Lower extremity	Time	910.07	2	455.03	33.56	.000	S
	Group*Time	64.01	6	10.67	0.79	.583	NS
FMA Total	Time	7283.95	2	3641.97	47.61	.000	S
	Group*Time	1446.48	6	241.08	3.15	.008	S
NIHSS	Time	799.59	2	393.79	40.75	.000	S
	Group*Time	85.92	6	14.32	1.46	.203	NS
MBI	Time	13331.52	2	6665.76	75.70	.000	S
	Group*Time	2254.59	6	375.77	4.27	.001	S
FIM	Time	9950.21	2	4975.11	59.62	.000	S
	Group*Time	1533.92	6	255.65	3.06	.010	S
9HPT	Time	12277.83	2	6318.91	14.98	.000	S
	Group*Time	533.35	6	889.73	2.17	.055	NS
mRS	Time	10.69	2	5.35	7.71	.001	S
	Group*Time	1.55	6	0.26	0.37	.894	NS
EQ-5D	Time	20.51	2	10.25	4.52	.014	S
	Group*Time	36.10	6	6.02	2.65	.022	S
MAS Elbow	Time	0.96	2	0.48	2.43	.094	NS
	Group*Time	1.65	6	0.28	1.40	.226	NS
MAS Ankle	Time	0.59	2	0.29	1.71	.088	NS
	Group*Time	1.18	6	0.20	1.15	.345	NS
Griptest Dominant hand	Time	52.03	2	26.01	0.85	.433	NS
	Group*Time	152.97	6	25.50	0.83	.550	NS
Griptest NonDominant -hand	Time	101.67	2	50.83	1.70	.189	NS
	Group*Time	106.96	6	17.83	0.60	.732	NS
APBrecording Cortical	Time	234.74	2	117.37	3.07	.052	NS
stim latency	Group*Time	319.45	6	53.24	1.39	.229	NS
APBrecording Cortical	Time	842196.62	2	421098.31	2.66	.077	NS
stimAmplitude	Group*Time	18.6621.834	6	301103.64	1.90	.092	NS
AHrecording Cortical	Time	130.68	2	66.34	0.40	.670	NS
stim latency	Group*Time	679.84	6	113.31	0.70	.652	NS
AHrecording Cortical	Time	26926.60	2	13463.30	0.35	.708	NS
StimAmplitude	Group*Time	254560.64	6	42426.77	1.094	.374	NS

df indicates degrees of freedom. NS, not significant; S significant

Table 6 Variable value changes (week 0 vs. week 3, week 0 vs. week 7) by ANOVA

Groups	Group(N)	Week0 vs week3				Week0 vs week7			
		Difference M±SD	95% CL of the Difference	F Scheffé post hoc test	*p*	Difference M±SD	95% CL of the Difference	F Scheffé post hoc test	*p*
FMA Upper Extremity	CG(n=12)	5.17±10.53[a]	-1.52, 11.86	3.68 c > d	.020	5.83±11.30[a]	-1.34, 13.01	4.32 a < c > d	.010
	SAG(n=11)	9.09±8.60[b]	3.32, 14.87			13.18±15.72[b]	2.62, 23.74		
	rTMSG(n=8)	17.00±13.89[c]	5.39, 28.61			23.38±14.70[c]	11.09, 35.66		
	SAEM-CSG(n=11)	2.27±7.28[d]	-2.62, 7.16			5.00±6.80[d]	0.43, 9.57		
FMA Lower Extremity	CG(n=12)	5.17±4.17	2.51, 7.82	0.23	.875	5.33±6.40	1.27, 9.40	0.66	.580
	SAG(n=11))	6.00±4.67	2.86, 9.14			5.27±4.41	2.31, 8.23		
	rTMSG(n=8)	4.88±6.49	-0.55, 10.30			8.63±5.24	4.25, 13.00		
	SAEM-CSG(n=11)	4.18±5.65	0.38, 7.98			5.91±6.50	1.54, 10.28		
FMA Total	CG(n=12)	10.33±12.87	2.16, 18.51	2.27	.096	11.17±13.07[a]	2.87, 19.47	4.02 a < c > d	.014
	SAG(n=11)	15.09±11.89	7.11, 23.08			18.45±17.01[b]	7.02, 29.88		
	rTMSG(n=8)	21.88±17.67	7.10, 36.65			32.13±17.27[c]	17.68, 46.57		
	SAEM-CSG(n=11)	6.45±12.11	-1.68, 14.59			10.91±12.43[d]	2.56, 19.26		
NIHSS	CG(n=12)	-0.17±3.46	-2.36, 2.03	2.70	.059	-1.50±2.32	-2.97, -0.03	2.57	.069
	SAG(n=11)	-2.64±2.69	-4.45, -0.83			-2.36±2.46	-4.02, -0.71		
	rTMSG(n=8)	-2.25±1.75	-3.72, -0.78			-3.13±1.73	-4.57, -1.68		
	SAEM-CSG(n=11)	-0.18±1.89	-1.45, 1.09			-0.55±1.92	-1.83, 0.74		
MBI	CG(n=12)	6.83±13.16[a]	-1.53, 15.20	3.51	.024	15.92±11.94[a]	8.33, 23.50	5.58	.003

	SAG(n=11)	14.36±11.74[b]	6.48, 22.25			18.64±18.21[b]	6.41, 30.87		
	rTMSG(n=8)	25.75±10.01[c]	17.38, 34.12	a < c		43.50±16.64[c]	29.59, 57.41	a < c	
	SAEM-CSG(n=11)	15.55±14.98[d]	5.48, 25.61			23.00±16.12[d]	12.17, 33.83	b < c	
FIM	CG(n=12)	7.17±13.54	-1.43, 15.77	2.17	.108	13.50±11.44[a]	6.23, 20.77	4.36	.010
	SAG(n=11)	10.64±8.63	4.84, 16.43			15.09±15.12[b]	4.94, 25.25		
	rTMSG(=8)	22.38±4.66	18.48, 26.27			36.13±6.88[c]	30.38, 41.87	a < c	
	SAEM-CSG(n=11)	15.91±21.14	1.71, 30.11			22.18±20.84[d]	8.18, 36.18	b < c	
9-HPT	CG(n=12)	-27.06±33.08	-48.08, -6.04	1.63	.199	-34.93±37.61	-58.83, -11.04	2.48	.076
	SAG(n=11)	-1.84±3.63	-4.28, 0.60			-0.49±3.76	-3.02, 2.04		
	rTMSG(n=8)	-25.45±34.42	-54.22, 3.32			-40.19±35.61	-69.96, -10.42		
	SAEM-CSG(n=11)	-18.70±36.07	-42.94, 5.53			-17.34±51.43	-51.89, 17.21		
AHSA-NOMS	CG(n=12)	0.17±0.58	-0.20, 0.53	1.45	.243				
	SAG(n=11)	0.27±1.01	-0.41, 0.95						
	rTMSG(n=8)	0.13±2.03	-0.57, 2.82						
	SAEM-CSG(n=11)	0.18±0.75	-0.32, 0.69						
FAC	CG(n=12)	0.42±1.00	-0.22, 1.05	1.29	.291				
	SAG(n=11)	1.45±1.51	0.44, 2.47						
	rTMSG(n=8)	1.25±1.04	0.38, 2.12						
	SAEM-CSG(n=11)	1.00±1.61	-0.08, 2.08						
mRS	CG(n=12)	0.00±1.21	-0.77, 0.77	0.62	.607	-0.58±1.00	-1.22, 0.05	0.20	.897
	SAG(n=11)	-0.27±1.42	-1.23, 0.68			-0.91±1.76	-2.09, 0.27		
	rTMSG(n=8)	-0.75±1.16	-1.72, 0.22			-1.00±0.76	-1.63, -0.37		
	SAEM-CSG(n=11)	-0.18±1.08	-0.91, 0.54			-0.73±1.49	-1.73, 0.27		
EQ-5D	CG(n=12)	9.83±1.64	8.79, 10.88	0.94	.429	9.67±2.61	8.01,	1.00	.403

								11.32	
	SAG(n=11)	10.91±2.34	9.33, 12.48			11.45±2.42	9.83, 13.08		
	rTMSG(n=8)	11.00±2.27	9.10, 12.90			10.13±1.46	8.91, 11.34		
	SAEM-CSG(n=11)	9.73±2.65	7.95, 11.51			10.18±3.19	8.04, 12.32		
K-MMSE	CG(n=12)	0.00±3.07	-1.95, 1.95	1.42	.253				
	SAG(n=11)	-0.09±3.70	-2.58, 2.39						
	rTMSG(n=8)	0.38±2.07	-1.35, 2.10						
	SAEM-CSG(n=11)	2.09±1.92	0.80, 3.38						
MAS Elbow	CG(n=12)	0.08±0.51	-0.24, 0.41	0.95	.424	0.08±0.51	-0.24, 0.41	3.02	.041
	SAG(n=11)	0.09±0.54	-0.27, 0.45			-0.09±0.70	-0.56, 0.38		
	rTMSG(n=8)	0.50±0.53	0.05, 0.95			0.63±0.74	0.00, 1.25		
	SAEM-CSG(n=11)	0.18±0.75	-0.32, 0.69			-0.09±0.30	-0.29, 0.11		
MAS Ankle	CG(n=12)	0.08±0.51	-0.24, 0.41	1.38	.265	0.00±0.43	-0.27, 0.27	1.11	.357
	SAG(n=11)	-0.09±0.83	-0.65, 0.47			0.00±0.77	-0.52, 0.52		
	rTMSG(n=8)	0.50±0.53	0.05, 0.95			0.38±0.52	-0.06, 0.81		
	SAEM-CSG(n=11)	0.18±0.60	-0.22, 0.59			-0.09±0.54	-0.45, 0.27		
Griptest Dominant – hand	CG(n=12)	-2.25±7.53	-7.04, 2.54	1.10	.362	-1.67±7.11	-6.19, 2.85	0.60	.619
	SAG(n=11)	4.64±14.29	-4.96, 14.24			1.45±6.58	-2.96, 5.87		
	rTMSG(=8)	2.75±8.19	-4.10, 9.60			1.75±7.19	-4.26, 7.76		
	SAEM-CSG(n=11)	1.18±4.58	-1.89, 4.26			0.91±5.94	-3.08, 4.90		
Griptest NonDominant –hand	CG(n=12)	1.50±9.79	-4.72, 7.72	0.34	.795	4.92±16.23	-5.40, 15.23	0.42	.742
	SAG(n=11)	0.45±4.08	-2.29, 3.20			0.55±4.25	-2.31, 3.40		
	rTMSG(n=8)	3.38±6.57	-2.12, 8.87			1.38±7.50	-4.90, 7.65		
	SAEM-CSG(n=11)	0.82±3.71	-1.67, 3.31			1.82±5.86	-2.12, 5.76		
APBrecording Cortical stim latency	CG(n=12)	-1.93±6.54	-6.08, 2.23	1.01	.401	-1.94±7.16	-6.49, 2.61	2.37	.085
	SAG(n=11)	2.17±7.54	-2.90, 7.24			2.06±6.91	-2.58, 6.71		
	rTMSG(n=8)	5.34±10.58	-3.51, 14.18			8.84±12.66	-1.75, 19.42		
	SAEM-	2.37±12.60	-6.09, 10.84			4.50±10.16	-2.32,		

	CSG(n=11)						11.32		
APBrecording Cortical stim Amplitude	CG(n=12)	151.33±421.80	-116.66,419.33	2.08	.119	15.00±252.13	-145.20, 175.20	0.81	.495
	SAG(n=11)	34.91±130.93	-53.05, 122.87			120.09±630.49	-303.48, 543.66		
	rTMSG(=8)	109.75±138.34	-5.90, 225.40			253.75±573.24	-225.49, 732.99		
	SAEM-CSG(n=11)	-310.73±808.53	-853.90,232.45			305.73±442.54	84.30, 603.03		
AHrecording Cortical stim latency	CG(n=12)	3.27±22.33	-10.92, 17.46	0.23	.873	-0.65±2.31	-2.11, 0.81	0.68	.568
	SAG(n=11)	-0.03±21.05	-14.17, 14.11			0.40±20.92	-13.66, 14.46		
	rTMSG(n=8)	-4.61±20.52	-21.77, 12.54			7.84±20.38	-9.20, 24.87		
	SAEM-CSG(n=11)	0.54±18.52	-11.90, 12.98			0.71±1.25	-0.13, 1.55		
AHrecording Cortical stim Amplitude	CG(n=12)	353.73±586.08	-18.65, 726.11	1.10	.362	-39.08±325.71	-246.03, 167.87	0.94	.430
	SAG(n=11)	149.78±214.39	5.75, 293.81			111.36±266.37	-67.59, 290.32		
	rTMSG(=8)	83.04±150.54	-42.82, 208.89			-103.13±305.58	-358.60, 152.35		
	SAEM-CSG(n=11)	156.20±264.08	-21.21, 333.61			26.36±279.46	-161.38, 214.11		

CG, control group; SAG, SA group; rTMSG, rTMS group; SAEM-CSG, SAEM-CS group

Table 7 Multiple comparisons of FMAUE, FMAT, MBI, FIM scores (week 0 vs. week 3)

Groups (total n=42)	FMAU *p* value	FMAT *p* value	MBI *p* value	FIM *p* value
SAG vs CG	.419	.281	.109	.497
rTMSG vs CG	.069	.153	**.005**	**.030**
SAEM-CSG vs CG	.238	.228	.277	.216
SAG vs SAEM-CSG	**.050**	.087	.646	.921
rTMSG vs SAEM-CSG	**.026**	.069	**.043**	.063
SAG vs rTMSG	.147	.321	.057	**.004**

CG, control group ; SAG, SA group ; rTMSG, rTMS group; SAEM-CSG, SAEM-CS group

p values were determined by Mann-Whitney U Test

Table 8 Multiple comparisons of FMAUE, FMAT, MBI, FIM scores (week 0 vs. week 7)

Groups (total n=42)	FMA Upper Extremity *p* value	FMATotal *p* value	MBI *p* value	FIM *p* value
SAG vs CG	.494	.459	.666	.758
rTMSG vs CG	**.015**	**.023**	**.002**	**<.001**
SAEM-CSG vs CG	.757	.497	.255	.267
SAG vs SAEM-CSG	.197	.236	.669	.693
rTMSG vs SAEM CSG	**.016**	**.012**	**.026**	**.012**
SAG vs rTMSG	.374	.266	**.016**	**.008**

CG, control group ; SAG, SA group ; rTMSG, rTMS group; SAEM-CSG, SAEM-CS group

p values were determined by Mann-Whitney U Test

Figures

	Enrolment	Allocation		Post-Allocation		Close-out
Time point	$visit_1$		$visit_2$~$visit_6$	$visit_7$~$visit_{11}$	$visit_{12}$~$visit_{16}$	$visit_{17}$
	week		1	2	3	
Enrolment						
Informed consent	X					
Demographic characteristics	X					
Medical history	X					
Vital signs	X					
Inclusion/exclusion criteria	X					
Random allocation		X	X			
Treatment			←	—	→	
Assessment						
Change of medical history			X		X	X
Safety assessment			X		X	X
FMA			X		X	X
NIHSS			X		X	X
MBI			X		X	X
FIM			X		X	X
K-MMSE			X		X	
9 HPT			X		X	X
ASHA-NOMS			X		X	
FAC			X		X	
EQ-5D			X		X	X
MAS			X		X	X
Hand Grip Strength Test			X		X	X
MEP			X		X	X
mRS	X		X		X	X

Figure 1

Standard Protocol Items: Recommendations for interventional Trials Statement (SPIRIT). The figure shows the enrollment, interventions, and data collection protocols.

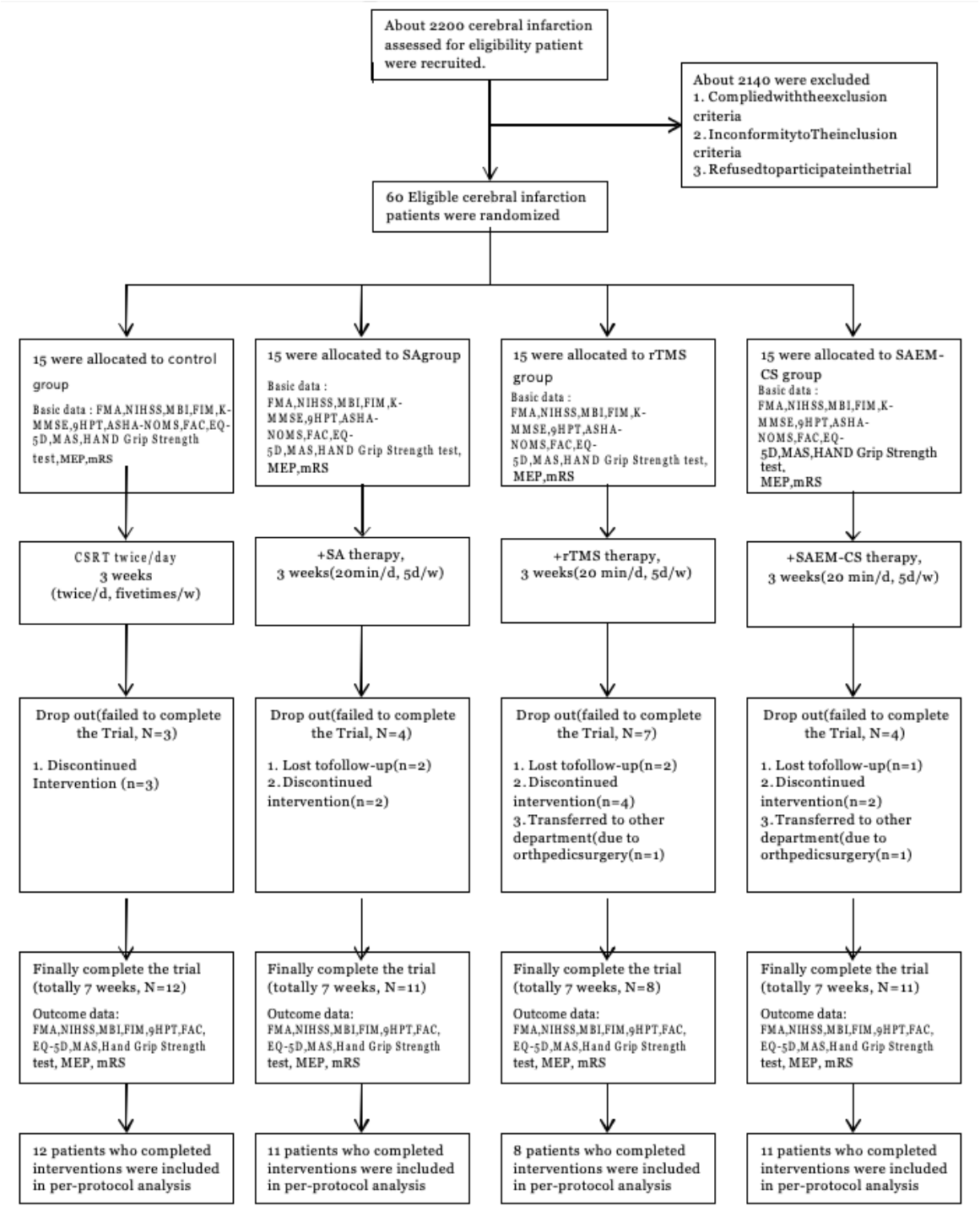

Figure 2

Consolidated Standards of Reporting Trials (CONSORT) diagram The flow of participants through the trial and the reasons for participant dropout are shown.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TrialsCONSORT2010Checklistadditionalfile1.doc