The Effect of Continuous Theta-Burst Transcranial Magnetic Stimulation Combined with Prism Adaptation on the Neglect Recovery in Stroke Patients

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Objectives: This study was designed to investigate the effect of prism adaptation (PA) combined with continuous theta-burst transcranial magnetic stimulation (cTBS) on the neglect recovery of stroke patients with unilateral neglect. *Methods*: A total of 14 stroke patients with unilateral neglect were randomly assigned to 2 groups including an intervention group undergone PA combined with cTBS over the left intact parietal cortex and a control group. PA combined with sham cTBS was perfomed for 2 weeks in 10 daily sessions. Before and after the intervention, patients were evaluated for visuospatial neglect measured using the Star Cancellation Test (SCT), Line Bisection Task (LBT), Figure Copying Test, and Clock Drawing Task. Neurological function was evaluated using the Modified Rankin Scale (MRS). *Results*: Both groups (PA alone and PA+ cTBS) showed improvement in their neglected symptoms (measured by SCT, LBT, Figure Copying Test, and Clock Drawing Task), and in their disability in the neurological function (measured by MRS) ($P < .05$). *Conclusions*: The results of the present study showed that, transcranial magnetic stimulation did not increase the effect of PA on neglect symptoms in stroke patients.

Key Words: Stroke—neglect—theta-burst transcranial magnetic stimulation—prism—recovery

Introduction

Over half of the patients with right brain stroke suffer from visuospatial unilateral neglect. Neglect is an independent and important poor prognostic factor after incidence of stroke. Often associated with neglect, several modalities of neglect recovery may occur including visual, motor, and spatial.[1-5] Pharmacological and nonpharmacological interventions have been applied with various success rates. Nonpharmacological treatments include left-hand somatosensory stimulation by visual scanning training,[6] optokinetic stimulation,[7] trunk rotation,[8] galvanic vestibular stimulation,[9] mirror,[10] transcranial direct stimulation,[11] Prism Adaptation (PA),[12] and recently transcranial magnetic stimulation (TMS).[13]

TMS has been shown promising results for recovery of unilateral neglect,[13-23] and has also been coupled with other techniques to improve the neglect recovery.[13,14,24-26] PA, as another nonpharmacologic technique has reliably improved ipsilateral attention bias and quality of life in neglect patients[27-29] either used singularly or combined with other recovery methods such as virtual reality, wheelchair driving, and mobility recovery. However, the combination of TMS with PA has not been evaluated so far.

To investigate the efficacy of TMS addition to PA in neglect recovery, a pilot study was designed and conducted on stroke patients with right hemispheric injury and neglect signs and symptoms. An applicale TMS protocol[24] was used, implemetation of which took less than

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1 minute in each session, found to be efficacious in improving the neglect. To measure the neglect, behavioural tests were used, like Star Cancellation Test, Line Bisection Task, Figure Copying Test, and Clock Drawing Scale asking patients about their daily activities impaired due to the neglect. Change in these scores was our primary outcome of treatment. We hypothesized that, TMS stimulation would boost PA effect in improving neglect tests' scores.

Methods

This interventional, pilot study was conducted in the Stroke Unit of Shariati Hospital, affilated to Tehran University of Medical Sciences, Tehran, Iran from August 2017 to September 2018.

Subjects

Inclusion criteria were stroke patients with neglect, diagnosis of whom was verified by magnetic resonance imaging, and clinical examination, being right handed and having informed consentfor participation in the study. The exclusion criteria were brain trauma, epilepsy, implanted heart pacemaker, cerebral edema, pain, and age less than 18 and more than 80 years old. The eligible patients were randomly assigned to 2 groups for visuospatial neglect recovery using PA[12] with mirror[10] involving intact limb activation, as descried elsewhere. Briefly, all the patients were asked to wear a pair of prism glasses with a rightward prismatic shift of 10° when the patients were asked to actively move their intact hand in front of a vertical mirror box (35 × 5 × 35 cm) for 20 minutes. In addition to PA, 1 group of patients received 10 sessions of TMS over the intact left posterior parietal cortex and the other group received 10 sessions of sham TMS over the same cortex. Patients were unaware of the group assignments; they were informed that they are going to undergo the treatment for their visuospatial neglect of left side of their body. However, therapist was aware about the patients' group allocation. Each patient was under treatment for 2 weeks, 10 sessions per day, and the assessments were done before and after the recovery sessions. A total of 14 subjects completed the treatment course out of 15 subjects enrolled.

TMS

Continous theta-burst transcranial magnetic stimulation (cTBS) was used over the left posterior parietal cortex (P3). We used a MagPro X100 machine (Magventure Company, Farum, Denmark) equipped with a commercially available figure of 8 coil for TMS. intervention (PA+ cTBS) group received cTBS inhibitory protocol once per day, for 10 sessions. The inhibitory protocol[24] consisted of 801 pulses delivered in 267 bursts. Each burst involved 3 pulses at 30 Hz, repeated with an inter burst interval of 100 ms. Stimulation was applied over the left posterior parietal cortex P3 in the 10/20 EEG system at an intensity of 80% RMT. The coil center was positioned tangentially over the P3 and its handle was positioned posteriorly and downward. Sham TMS followed the same protocol except the coil was positioned at 90° angle to the skull, and a small part of the coil was resting on the skull. Participants were blind to the type of therapy. These patients tolerated cTBS treatment using 8-coil without any side effects.

Assessments

The outcome was unilateral neglect measured using the Star Cancellation Task (SCT),[30] and the Line Bisection Task (LBT),[31,32] Figure Copying Test,[33] Clock Drawing,[34] and neurological function was evaluated using the Modified Rankin Scale (MRS).[35]

In the SCT, participants were required to mark a total of 50 little stars scattered between 50 big stars. A star ratio was calculated with the numerator as the little stars marked on the left side of the test page and the denominator as the total little stars marked.

In the LBT, participants were instructed to bisect 40 horizontal lines including 18 lines on the middle, 10 lines on the right side, and 12 lines on the left side on an A4 paper. The absolute distance between the patient's bisection and the middle lines' points was computed. We also calculated another score which was ratio of the number of lines on the left side of the page detected by the patient.

In the Figure Copying Test, the patients were asked to copy a multiobject scene consisting of 5 figures on an A4-sized plain paper. Omission of at least 1 of the left-sided features of each figure was scored as 1, and negligence of each whole figure was scored as 2. One additional or preservation point was given when left-sided figures were drawn on the right side. Thus, the maximum score was 10. In the extreme case, if a figure omits all 5 figures, then the score would be 10. A score of 2 would indicate that a figure has omitted 1 object entirely. A score of 1 would indicate that the left half of 1 figure has been neglected and in addition, a left-sided object on the right side of the paper sheet has been copied. A score obtained higher than 1 was considered as negligence.

In the Clock Drawing, the patients were asked to copy a multiobject scene consisting of clock on an A4-sized plain paper. Error on omission of at least 1 of each item was scored as 1. Error items included: in the clock size: the clock with small size error. Clock shape: the clock with an elliptical contour error. Horizontal placement: clock shape was placed more rightward. Radial placement: the clock shape drawn more distally. Overall displacement: distance from center regardless of the directional placement. Clock Drawing accuracy: these items all refer to errors of omission in hand, quality, and numbers. Its scores ranged from 0 to 8.

The MRS was translated and validated in our previous study. In this questionnaire, patients are enquired about their independence in the activities of daily living (ADL). It

involves an approximate evaluation of independence in 6 real life situations. A score of 0-1 denotes full function, a score of 2-3 shows mild impairment and movement with a cane, a score of 4 represents severe impairment, and a score of 5 signifies total dependence and completed bed rest.

Ethical Considerations

The study was approved by the Ethics Committee of Iran University of Medical Sciences [IR.IUMS.REC.1396.93012334], and was registered at the Iranian Registry of Clinical Trials [IRCT20170423033606N3], accessible at https://www.irct.ir. An informed consent was obtained from all the subjects at the time of study enrollment.

Statistical Analysis

Student's *t* test and Fisher's exact test was used to compare the groups (PA+ cTBS versus PA+ sham cTBS) in continuous and dichotomous variables, respectively. Then, repeated-measures analysis of variance (ANOVA) was performed between the values of SCT, LBT, Figure Copying Test, Clock Drawing, and MRS, with group (PA+ cTBS versus PA+ sham cTBS) as between-subject main factor and time (postintervention versus preintervention) as within subject main factor. In each ANOVA model, TMS was assumed effective if group × time interaction was found significant indicating more score changes in 1 group compared to another. For all statistical analyses, a *P* value of less than .05 was considered as statistically significant.

Results

Subjects' Characteristics

Baseline characteristics of the participants are summarized in Table 1. The mean age of patients was equal to 65 years old, they were mostly male (70%), and had on average 10 years of education. Ischemic type of stroke was the cause of disability in 8 of patients, and stroke onset date was within the last 6 months prior to randomization in 40% of patients. There was no difference in age, sex, education level, symptom duration, and type of stroke between PA+ cTBS and PA+ sham cTBS patients (Table 1).

Change in the Neglect Scores

Descriptive statistics of neglect scores before and after the treatment are provided at Table 2. In a repeated ANOVA model with the SCT, LBT, Figure Copying Test, and Clock Drawing Scores as the outcome variable, the time factor was significant (in the SCT, $F = 42.381$, $P < .001$), (in the LBT, $F = 31.630$, $P < .001$), (in the NL, $F = 123.838$, $P < .001$), (in the Figure Copying Test, $F = 64.438$, $P < .001$) and (in the Clock Drawing $F = 10.690$, $P < .001$), indicating that SCT, LBT, NL, Figure Copying Test, and Clock Drawing Scores improved in both groups, and patients were improved in terms of neglect symptoms after the recovery (Table 2, Fig 1). Table 2 shows means of neglect variable scores in both PA+ cTBS and PA groups before and after 10 sessions of recovery. However, the both groups were not significantly different, as the group × time interaction was not significant indicating that neglect recovery happened more in 1 group compared to another.

Table 1. *Patient's characteristics**

Variables	PA (n = 7)	PA+ cTBS (n = 7)	*P* value*
Age (y) mean ± SD	65.5 ± 10.2	67.5 ± 8.4	*P* = .69
Sex (M: F) no. (%)	5 (70): 2 (30)	5 (70): 2 (30)	*P* = 1.00
Type of stroke: transient ischemic attack no. (%)	4 (57.1)	4 (57.1)	*P* = .70
Type of stroke: intracranial hemorrhage no. (%)	3 (42.1)	3 (42.1)	*P* = .70
Time since stroke onset: subacute no. (%)	3 (42.9)	3 (42.9)	*P* = .70
Time since stroke onset: chronic no. (%)	4 (57.1)	4 (57.1)	*P* = .70
Region of stroke: cortex parietal no. (%)	4 (57.1)	4 (57.1)	*P* = .70
Region of stroke: cortex temporal no. (%)	5 (71.4)	4 (57.1)	*P* = .50
Region of stroke: cortex frontal no. (%)	3 (42.9)	3 (42.9)	*P* = .50
Region of stroke: subcortex no. (%)	3 (42.9)	3 (42.9)	*P* = .70
Grade school education mean ± SD	11.1 ± 2.2	8.0 ± 2.4	*P* = .35
Activities daily living measurements: the modify ranking scales mean ± SD	3.4 ± .5	4 ± .5	*P* = .12
Neglect measurements:			
Number of lines in left side mean ± SD.	1.7 ± 2.6	4.1 ± 4.3	*P* = .45
Line Bisection Task mean ± SD.	27.6 ± 11.6	33.7 ± 15.6	*P* = .62
Star Cancellation Test mean ± SD.	16.4 ± 11.3	21.5 ± 9.7	*P* = .38
Clock Drawing mean ± SD.	4.8 ± 3.4	6.1 ± 2.7	*P* = .53
Figure Copying Test mean ± SD.	3.7 ± 2.7	6.1 ± 1.2	*P* = .07

*Dichotomous variables are compared with Fisher's exact test, quantitative variabes with *t* test, and non-normal quantitative variabes with Mann-Whitney.

Table 2. *Visuospatial neglect measurement before and after the rehabilitation*

Neglect measurements	Before intervention; mean ± (SD)		After intervention; mean ± (SD)		Repeated ANOVA	
	PA+ cTBS	PA	PA+ cTBS	PA	Time	Group × time factor
Star Cancellation Test	21.5 ± (9.7)	16.4 ± (11.3)	.5 ± (1.5)	2.4 ± (4.0)	***P* < .001*,****	*P* = .217
Line Bisection Test	33.7 ± (15.6)	27.6 ± (11.7)	6.7 ± (11.6)	5.6 ± (5.7)	***P* < .001*,****	*P* = .572
Number of lines on the left side	10.8 ± (1.8)	9.4 ± (4.2)	.5 ± (1.1)	.5 ± (.9)	***P* < .001*,****	*P* = .422
Figure Copying Test	6.1 ± (1.2)	3.7 ± (2.7)	1.2 ± (1.7)	.5 ± (.9)	***P* < .001*,****	*P*= .111
Clock Drawing	6.1 ± (2.7)	4.8 ± (3.4)	5 ± (2.3)	4 ± (3.4)	***P* = .007*,****	*P* = .649

Abbreviations: cTBS, continuous theta-burst transcranial magnetic stimulation; PA, prism adaptation.
Values are mean ± (SD).
*Significant difference between prerehabilitation and postrehabilitation of group at $P < .05$ by repeated ANOVA model, time factor.
**Significant difference between groups at $P < .05$ by repeated ANOVA model, the group × time factor.

ANOVA models were repeated with SCT, LBT, NL, Figure Copying Test, and Clock Drawing Scores as the outcome, and PA+ cTBS did not boost improvement in the SCT, LBT, NL, Figure Copying Test, and Clock Drawing Scores compared to the sham stimulation (in the SCT, F = 1.695, $P = .217$), (in the LBT, F = .338, $P = .572$), (in the NL, F = .690, $P = .422$), (in the Figure Copying Test, F = 2.959, $P = .111$), and (in the Clock Drawing, F = .218, $P = .649$) (Table 2, Fig 1).

Figure Copying Test and Clock Drawing Error Scores were detected with respect to the sum of error scores in the participants before and after recovery (Examples shown in Fig. 2 and 3).

Change in the Disability of Motor Function Scores

In a repeated ANOVA model with the MRS scores as the outcome variable, the time factor was significant (F = 14.635, $P = .002$), indicating that MRS scores improved in both groups, and patients were more functional after the recovery. Both groups were not significantly different, as the group × time interaction was not significant (F = .041, $P = .844$) indicating that functional recovery happened more in 1 group compared to another (Fig 1, Table 2). Table 2 shows means of MRS scores in both PA+ cTBS and PA+ sham cTBS groups before and after 10 sessions of recovery. The MRS scores decreased (disability of motor function symptoms improved) in both groups.

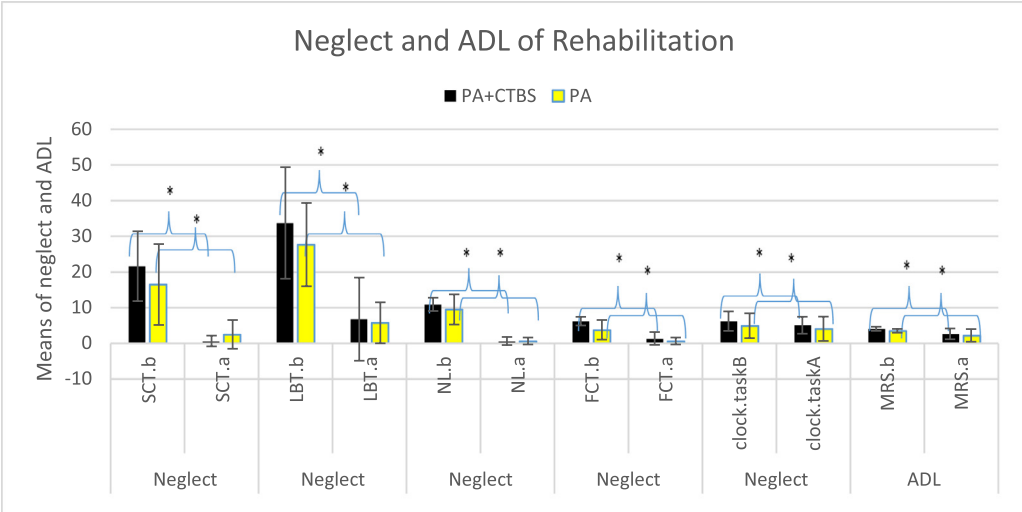

Figure 1. *Figure shows stroke patients' scores in the neglect symptoms and activities of daily living of rehabilitation before and after 10 sessions. Both groups, PA and PA+ cTBS show rehabilitation significantly in neglect (measured by SCT, LBT, NL, Figure Copying Test, and Clock Drawing) and ADL (measured by MRS). Error bars indicate standard deviation. Asterisks indicate results that were significant using repeated ANOVA model, time factor = group × time factor:* *P < .05.

Abbreviations: ADL, activities of daily living; clock task A, Clock Drawing after rehabilitation; clock task B, Clock Drawing before rehabilitation; cTBS, continuous theta-burst transcranial magnetic stimulation; FCT.a, Figure Copying Test after rehabilitation; FCT.b, Figure Copying Test before rehabilitation; LBT.a, Line Bisection Task after rehabilitation; LBT.b, Line Bisection Task before rehabilitation; MRS.a, Modified Rankin Scale after rehabilitation; MRS.b, Modified Rankin Scale before rehabilitation; NL.a, number of lines in left side after rehabilitation; NL.b, number of lines in left side before rehabilitation; PA, prism adaptation; SCT.a, Star Cancellation Test after rehabilitation; SCT.b, Star Cancellation Test before rehabilitation.

Figure 2. *The Figure Copying Test in patients with neglect in 2 groups (cTBS +PA, PA) used in this study. Figure on the left side of columns shows the response of the patients with neglect in Figure Copying Task at before intervention. Those on the right side of columns are examples of the response of the patients with neglect in figure copying after 10 sessions of rehabilitation.*

Discussion

In the pilot study, neglect and disability of motor function in stroke patients were improved after 10 sessions of recovery using a prism and prism combined with cTBS.

Nonpharmacological recovery approach has been explored for neglect aimed at recovering visuospatial perception and improving functional deficits.[36,37] Prism and mirror have been used in the neglect treatment as nonpharmacological treatments.[10,12] In a randomized trial, stroke patients who received mirror therapy for 4 weeks performed better at SCT during therapy and till 5 months after treatment cessation compared to the control group.[10] In contrast, PA has been used for neglect treatment with variable success. PA was useful in the neglect recovery in some clinical trials[38,39] and was not useful in some others.[40,41] TMS is another nonpharmacologic treatment which has been effective in the neglect recovery in several clinical trials.[13-23] Investigators have stimulated brain by 3 TMS protocols, and at least 1 study reported higher efficacy while employing cTBS.[42] Our study was novel as it combined 2 nonpharmacologic therapies in the neglect recovery. It was found that, combination of PA was effective in the neglect recovery and was not even more efficacious when combined with TMS.

Each of the therapies combined in our study has a different mechanism of action in the neglect recovery.

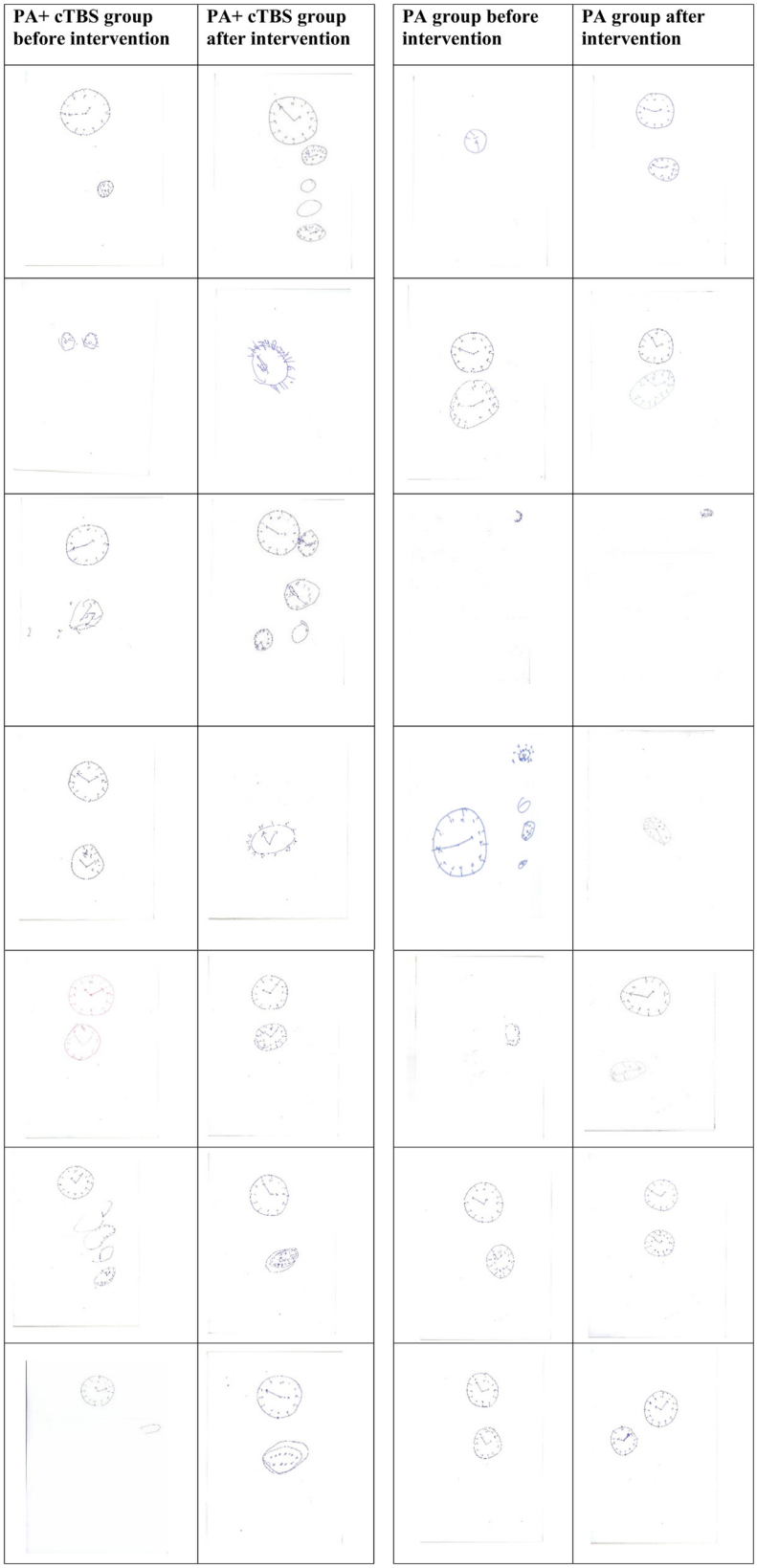

Figure 3. *The Clock Drawing in patients with neglect in 2 groups (cTBS +PA, PA) used in this study. Figure on the left side of columns shows the response of the patients with neglect in Clock Drawing Task at before intervention. Those on the right side of columns are examples of the response of the patients with neglect in Clock Drawing Task after 10 sessions of rehabilitation.*

Studies have found that, decreased affected hemisphere's excitability and increased intact hemisphere's excitability play a major role in the visuospatial neglect.[43] In fact, our cTBS protocol decreased excitability of the unaffected hemisphere leading to rebalancing the excitability of hemispheres.[44] However, PA works by shifting the attention to the left unattended side[38] and mirror therapy possibly works by creating a visual imagery activating mirror neurons.[10] This combination of recovery mechanisms may underlie the effect observed in our study. Likewise, in case of combination of TMS with sensory curing, a recovery was found in the neglect symptoms and ADL.[17]

Improvement in neglect and disabilities in performing the activities of daily living in stroke patients is a finding not generally found in the previous studies on neglect recovery. Although some clinical trials of unilateral neglect recovery did not report any functional evaluation,[42,44] some trials reported improvement in the stroke patient's functional disabilities with neglect targeted recovery[10,23] while some others did not.[17,37] We hypothesized that more brain areas were modulated through our combined treatment and this combination underlies functional benefits, which is difficult to observe in clinical trials with small sample sizes. However, more studies are needed using functional imaging to verify this hypothesis. In fact, in our previous study, we found that stimulation of 2 areas of brain (dorsolateral prefrontal and primary motor cortices) was more powerful than 1 area (primary motor cortex) in the recovery of stroke-related upper motor paresis.[45]

There were some limitations in our pilot study. The sample size was small and all came from 1 center. Patients were not followed for an extended time after the treatment to evaluate the long-term benefits. Although, it is noteworthy that 40% of our patients were in the subacute phase of stroke recovery. Likewise, improvement of neglect and ADL in the subacute and acute phases by TMS has been reported in some clinical trials.[13,17,23,25] Although there was no statistically significant difference in patient's baseline for onset time of chronic and acute phases after stroke among 2 groups (Table 1). The absence of cTBS alone group for comparison was also a limitation in this study, although continuous theta-burst TMS has been applied in a previous study.[15] The mean values of changes in neglect measurements obtained from postintervention minus those of preintervention were found to be higher in the PA+ cTBS group than in the PA group. Thus, it may be change in our result with large sample size. Finally, more research is needed to replicate our findings in a larger group of stroke patients and to uncover brain regions whose functions change after the rehabilitation with prism alone and prism combined with cTBS.

In future, studies with larger sample sizes and embedded functional imaging will help to verify more explicitly findings of this study. However, our study was the first clinical trial reported about the effects of a combination of 2 nonpharmacologic therapies on the neglect and ADL recovery.

Conclusions

The results of the present study showed that, both groups (PA alone and PA+ cTBS) improved in terms of their neglect symptoms and in their disability in the neurological function. Continuous theta-burst TMS did not increase the effect of PA on the neglect recovery in stroke patients.

Conflict of Interest

None.

Side Effects

Safety guideline for inhibitory protocol was used.[46] None of the patients reported any side effects and they tolerated the treatments.

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