Original article

High frequency repetitive transcranial magnetic stimulation versus sertraline in treatment of poststroke depression: A pilot study

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Background: Poststroke depression (PSD) has impact on rehabilitation outcome. Repetitive transcranial magnetic stimulation (rTMS) has been proven as a treatment of depression and might reduce depressive symptoms after stroke.

Objectives: To determine the effects of high frequency rTMS in treatment of PSD compared to sertraline. We also investigated the effects of rTMS combined with sertraline.

Methods: Fourteen patients with PSD were randomly allocated into 3 groups: 1) the rTMS group received 10 sessions of 10 Hz rTMS; 2) the sertraline group obtained sertraline 50 mg daily and sham rTMS; and, 3) the combined group received 10 Hz rTMS combined with sertraline 50 mg daily. Hamilton rating scale for depression (HAM-D) was assessed at baseline and week 2, 6 and 14. At baseline and week 6 and 14, modified Barthel Index (MBI) and Brunnstrom stages of stroke recovery were evaluated.

Results: The rTMS group showed significant reduction of HAM-D score at week 6 ($- 9.8 \pm 7.1$; $P < 0.05$) while the sertraline and combined groups did not show significant improvement ($- 9.2 \pm 1.0$ and $- 4.8 \pm 2.9$, respectively). HAM-D, response and remission rate, response and remission over the time, MBI and motor recovery among groups were not significantly different.

Conclusion: High frequency rTMS might have antidepressant effect in PSD. Its effect might not be different from sertraline. Benefit of rTMS given in combination with sertraline over rTMS or sertraline alone is still inconclusive.

Keywords: Stroke, depression, repetitive transcranial magnetic stimulation, sertraline.

Stroke is one of major public health concern. Approximately 30.0% of stroke patients have poststroke depression (PSD).[1, 2] PSD may lead to more deterioration of functional activities compared with stroke patients without depression [3 - 7] and may have impact on rehabilitation. Mechanism in which underlies PSD is still unknown. Physical impairments may be related to depression after stroke.[5]

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Several therapeutic interventions have been studied in PSD. Sertraline, a selective serotonin reuptake inhibitor (SSRI), has been widely prescribed [8] and found to be effective in treatment of PSD.[9, 10] However, serious adverse effects have been reported.[11, 12] Repetitive transcranial magnetic stimulation (rTMS) has been investigated for treatment of PSD over the past decades. rTMS device delivers magnetic field through TMS coil, generating electric field in the brain underneath the coil.[13] If high frequency ($\geq$ 5 Hz) stimulation is used, excitability of cortical area under the coil will be increased. In contrast, if low frequency stimulation ($\leq$ 1 Hz) is applied, decreased cortical excitability will be observed.[14] High frequency rTMS over the left

dorsolateral prefrontal cortex (DLPFC) has been proven as a treatment of depression.[15] Many studies reported superiority of high frequency rTMS over sham rTMS in PSD [16 - 18], but evidence of its benefit over antidepressant medication is insufficient.

Our aim of current study was to investigate the effects of high frequency rTMS over the left DLPFC, sertraline and combination of both treatments on depressive symptoms of subacute stroke patients with PSD. In addition, our secondary objectives were to study the effects of these interventions on functional independence and motor recovery. Adverse effects were also recorded.

Materials and methods

This trial was registered at the Thai Clinical Trials Registry (www.clinicaltrials.in.th) as TCTR 20180112001 and has been approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University as COA 494/2013. Written informed consent was given by all subjects.

Subjects

Stroke patients who were hospitalized in the Thai Red Cross Rehabilitation Center for rehabilitation were recruited. Inclusion criteria were: 1) aged ≥ 18 years; 2) within 6 months after stroke onset; 3) had evidence of ischemic stroke obtained from neuroimaging; 4) had depressive episode after the stroke onset according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM IV-TR); mood disorder due to medical condition (stroke); and, 5) antidepressive agent had not been given or had been withdrawn longer than 5 times of its half-life before the study enrollment.

Subjects were excluded if they: 1) had other neurological disorders, i.e. Parkinson's disease, dementia; 2) had depressive symptoms before the onset of stroke or had other psychiatric disorders; 3) were contraindicated to rTMS and/or sertraline; 4) were unable to communicate; or, 5) had cognitive impairment, scored < 23 on the Thai Mental State Examination (TMSE).

All subjects received in-patient rehabilitation for 6 weeks regarding their impairments and disabilities.

Subjects who did not present at any time point of follow up would drop out from the study.

Subjects who met eligibility criteria were allocated using block randomization by an investigator into: 1) rTMS group; 2) sertraline group; or, 3) combined group. Allocation sequence was sealed in envelopes. Other two investigators opened the envelopes and performed rTMS.

rTMS protocol

We used Magstim Rapid 2 system (Magstim Company Ltd., Whitland, UK) and 70-mm, air-cooled, figure-8 coil in this study. Subjects were asked to seat on a chair and wear earplugs. Right abductor pollicis brevis (APB) was chosen as a reference muscle for resting motor threshold (rMT) determination.

During rTMS sessions, the coil was placed over the left DLPFC, which was designated as a point 5 centimeters anterior to the right APB hot. In the rTMS and combined groups, the subjects received 10 Hz rTMS over the left DLPFC while placing the coil tangentially to the scalp in anteroposterior direction with handle of the coil held posteriorly and 45 degrees outward from midline. Twenty trains of rTMS, intensity 110.0% of the rMT for 5 seconds for each train with 60 second-intertrain interval were given, totally 1,000 pulses/session. The stimulation was performed 5 sessions a week, for a total of 10 sessions over 2 weeks.

In the sertraline group, sham rTMS was given. Same stimulus parameters were used but the coil was laid perpendicular to the scalp.

Sertraline

Subjects in the sertraline and combined groups received 50 mg of sertraline, once daily for 14 weeks. No placebo drug was given in the rTMS group.

Measurements

Baseline characteristics including age, sex, onset of stroke, side and location of the lesion, TMSE, National Institutes of Health Stroke Scale (NIHSS), marital and educational status were recorded before the study. Outcome measurements regarding depressive symptoms were recorded at baseline, week 2, 6 and 14. Functional independence and motor recovery were assessed at baseline, week 6 and 14.

Hamilton rating scale for depression

17-item Hamilton rating scale for depression – Thai version (HAM-D) [19] was used to assess depression severity. Response is determined as ≥ 50.0% reduction in baseline symptom severity which sustained for 3 consecutive weeks.[20, 21] Score of ≤ 7 for 3 consecutive weeks is used to define remission.[20, 21] Therefore, we identified response and remission at week 6 and 14. In current study, a psychologist, who was blinded to the allocation, was trained in using HAM-D by a psychiatrist and performed the evaluation of depression severity at baseline and each time point.

Secondary outcomes

Modified Barthel Index (MBI; Thai version) [22] was used to measure independence in activities of daily living (ADL). Motor recovery was determined by Brunnstrom stages of motor recovery.[23] Subject interviews and medical records were used to identify adverse events. All secondary outcomes were assessed by a blinded assessor.

Statistical analysis

In this study, both intention-to-treat and per-protocol analyses were conducted. In intention-to-treat analysis, missing data were imputed using last observation carried forward method. Data were expressed as mean ± standard deviation (SD) Baseline characteristics were analyzed using descriptive statistics. Regarding HAM-D and MBI scores, Friedman test with Nemenyi multiple comparison was used to compare scores within the same group, and Kruskal-Wallis test with Dunn's test was adopted to compare scores across groups. Fisher's exact test was used in analysis of Brunnstrom stages of motor recovery. Survival analysis was conducted in terms of response and remission. P - value < 0.05 was considered statistically significant. R-3.6.3 (R Foundation, Vienna, Austria) was used for Friedman test and Nemenyi multiple comparisons. STATA SE 15.0 (StataCorp LLC, College Station, TX, USA) was used for all other analyses.

Results

Among 30 patients recruited from the Thai Red Cross Rehabilitation Center, 14 of them were eligible to participate in this study (Figure 1). None of subjects previously received antidepressant medication. One subject in the combined group dropped out from the study in the first week due to unstable medical condition. Data retrieved from a total of 14 subjects were analyzed using intention-to-treat analysis. Baseline characteristics are shown in Table 1.

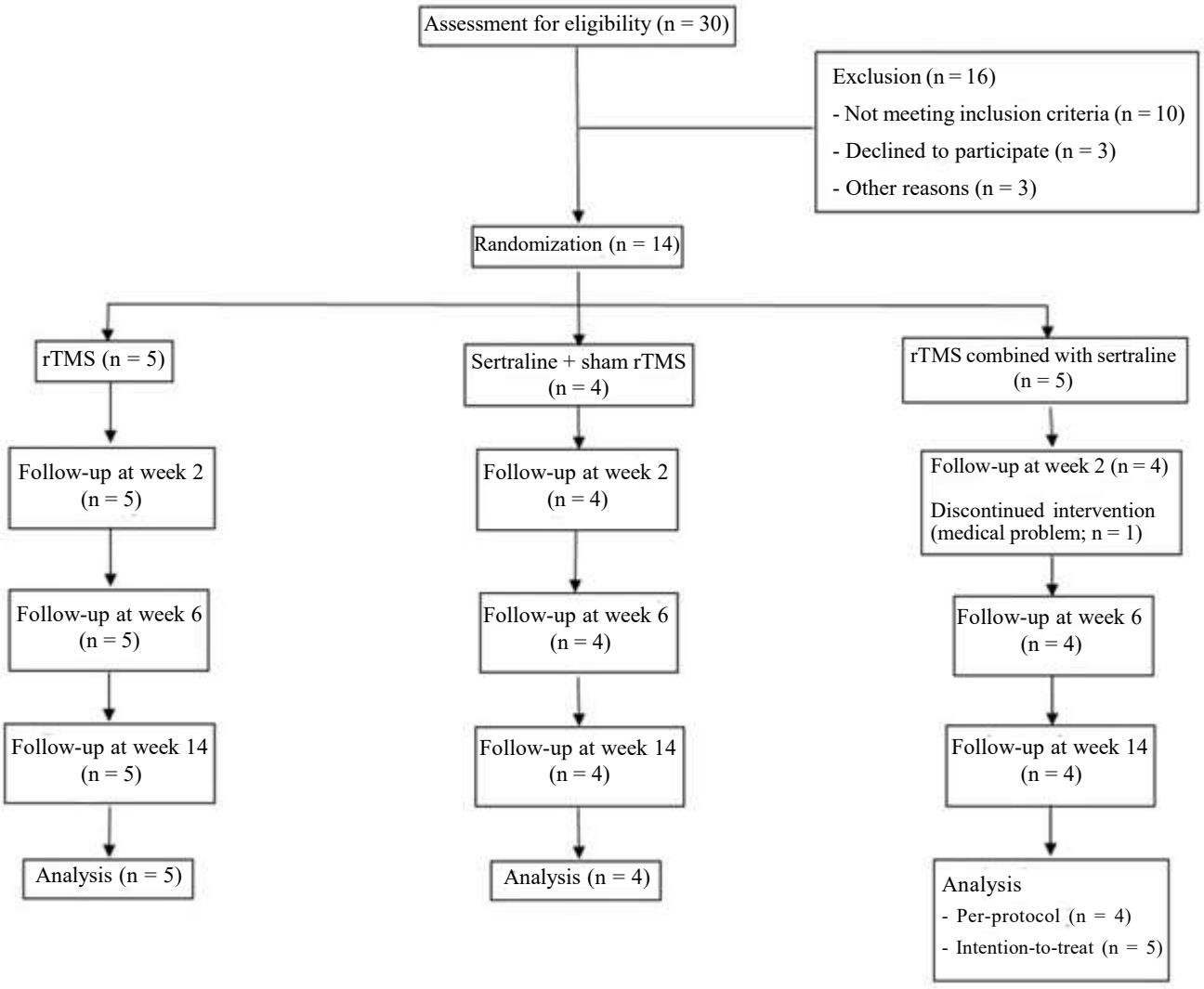

Figure 1. CONSORT flow diagram.

Table 1. Baseline characteristics.

	rTMS (n = 5)	Sertraline (n = 4)	Combined (n = 5)
Age (years), mean ± SD	65.0 ± 12.7	62.3 ± 8.5	60.6 ± 11.1
Gender, n (%)			
Male/Female	1 (20)/4 (80)	2 (50)/2 (50)	3 (60)/2 (40)
Lesion, n (%)			
Supra-/Infratentorial	4 (80)/1 (20)	3 (75)/1 (25)	5 (100)/0 (0)
Side of lesion, n (%)			
Right/ Left	3 (60)/2 (40)	2 (50)/2 (50)	2 (40)/3 (60)
Duration after onset (days), mean SD	78.6 ± 45	59.8 ± 45.5	34.0 ± 11.3
NIHSS, mean ± SD	8.2 ± 2.2	5.5 ± 4.7	8 ± 3.9
TMSE, mean ± SD	24.5 ± 1.9	27.8 ± 1.7	26.5 ± 0.7
HAM-D, mean ± SD	17.2 ± 5.9	14.0 ± 2.5	12.6 ± 5.5
MBI, mean ± SD	43.2 ± 21.2	68.3 ± 28.3	59.4 ± 26.1
Brunnstrom stages, n (%)			
Arm			
1/2/3	0 (0)/3 (60)/2 (40)	1 (25)/1 (25)/0 (0)	0 (0)/1 (20)/3 (60)
4/5/6	0 (0)/0 (0)/0 (0)	1 (25)/0 (0)/1 (25)	1 (20)/0 (0)/0 (0)
Hand			
1/2/3	1 (20)/3 (60)/1 (20)	2 (50)/ 0 (0)/0 (0)	4 (80)/0 (0)/1 (20)
4/5/6	0 (0)/0 (0)/0 (0)	0 (0)/ 1 (25)/1 (25)	0 (0)/0 (0)/0 (0)
Leg			
1/2/3	0 (0)/3 (60)/1 (20)	0 (0)/2 (50)/0 (0)	0 (0)/0 (0)/2 (40)
4/5/6	1 (20)/0 (0)/0 (0)	0 (0)/0 (0)/2 (50)	2 (40)/1 (20)/0 (0)
Underlying disease, n (%)			
Presence/ Absence	4 (80)/1 (20)	4 (100)/0 (0)	5 (100)/0 (0)
Marital status, n (%)			
Single	0 (0)	0 (0)	1 (20)
Married	5 (100)	4 (100)	4 (80)
Divorced	0 (0)	0 (0)	0 (0)
Widowed	0 (0)	0 (0)	0 (0)
Separated	0 (0)	0 (0)	0 (0)
Educational status, n (%)			
Primary school	5 (100)	2 (50)	2 (40)
Middle school	0 (0)	1 (25)	0 (0)
High school	0 (0)	0 (0)	0 (0)
College	0 (0)	1 (25)	1 (20)
University	0 (0)	0 (0)	2 (40)

HAM-D score is shown in Figure 2. Only the rTMS group demonstrated statistically significant improvement in HAM-D at week 6 (mean difference from baseline - 9.8 ± 7.1; $P < 0.05$) but the improvement was not significantly different among groups. Survival analysis also showed no statistically significant difference in terms of response or remission over the time among 3 groups (Figure 3). Response rate of the rTMS, sertraline and combined group were 60.0%, 75.0% and 80.0%, respectively. Remission rate of the rTMS, sertraline and combined group were 40.0%, 75.0% and 80.0%, respectively. Difference in response and remission rate among groups was not statistically significant.

Statistically significant improvement in activities of daily living was found only in the rTMS group in week 14 (Figure 2). However, when compared across groups, there was no statistically significant difference found. No statistically significant improvement in Brunnstrom stages of motor recovery within the same group was observed. Difference in motor recovery was not statistically significant among groups (Figure 4).

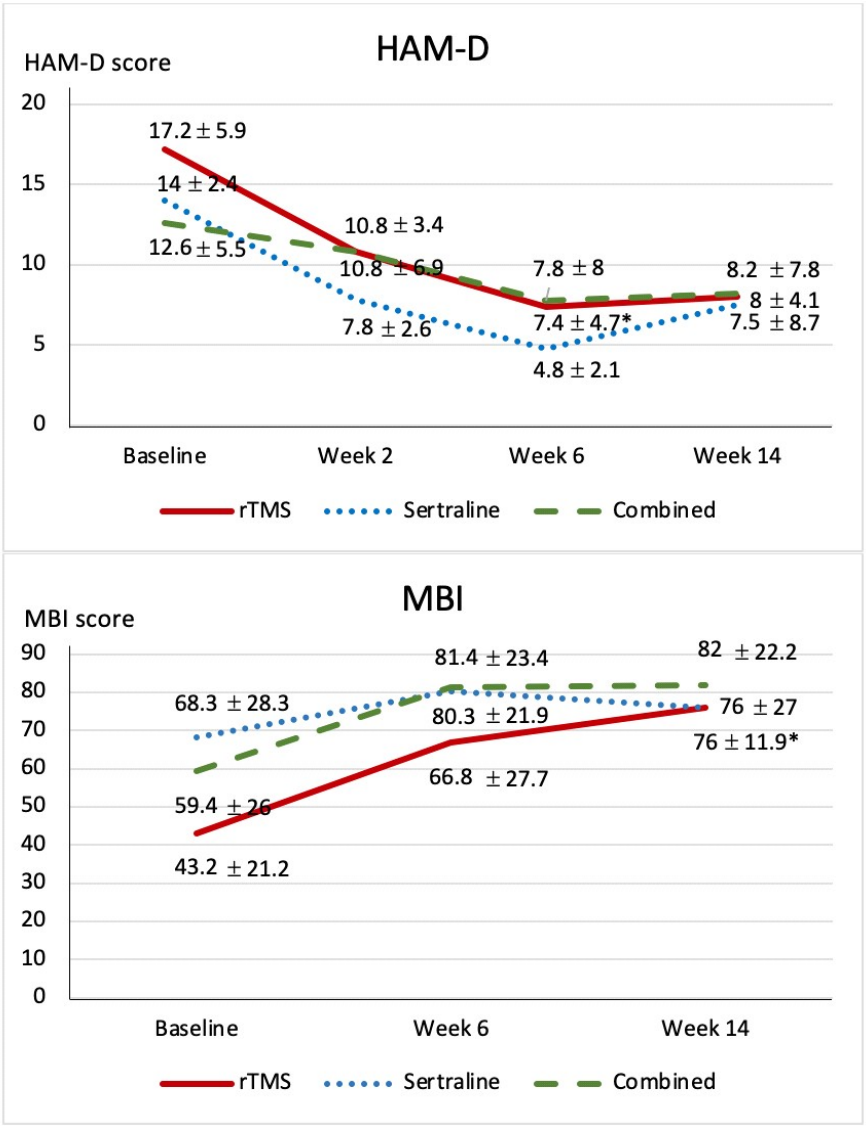

Figure 2. HAM-D and MBI.

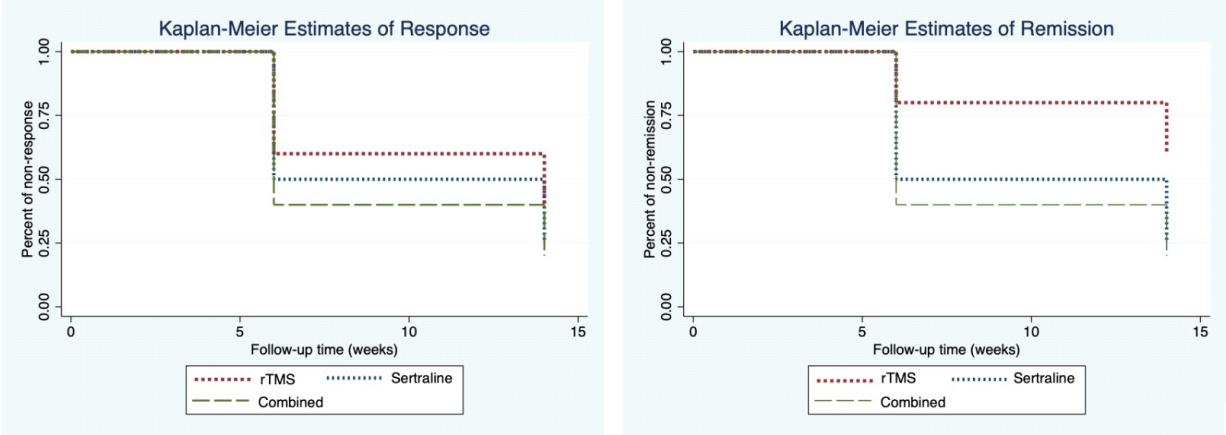

Figure 3. Kaplan-Meier curves of response and remission.

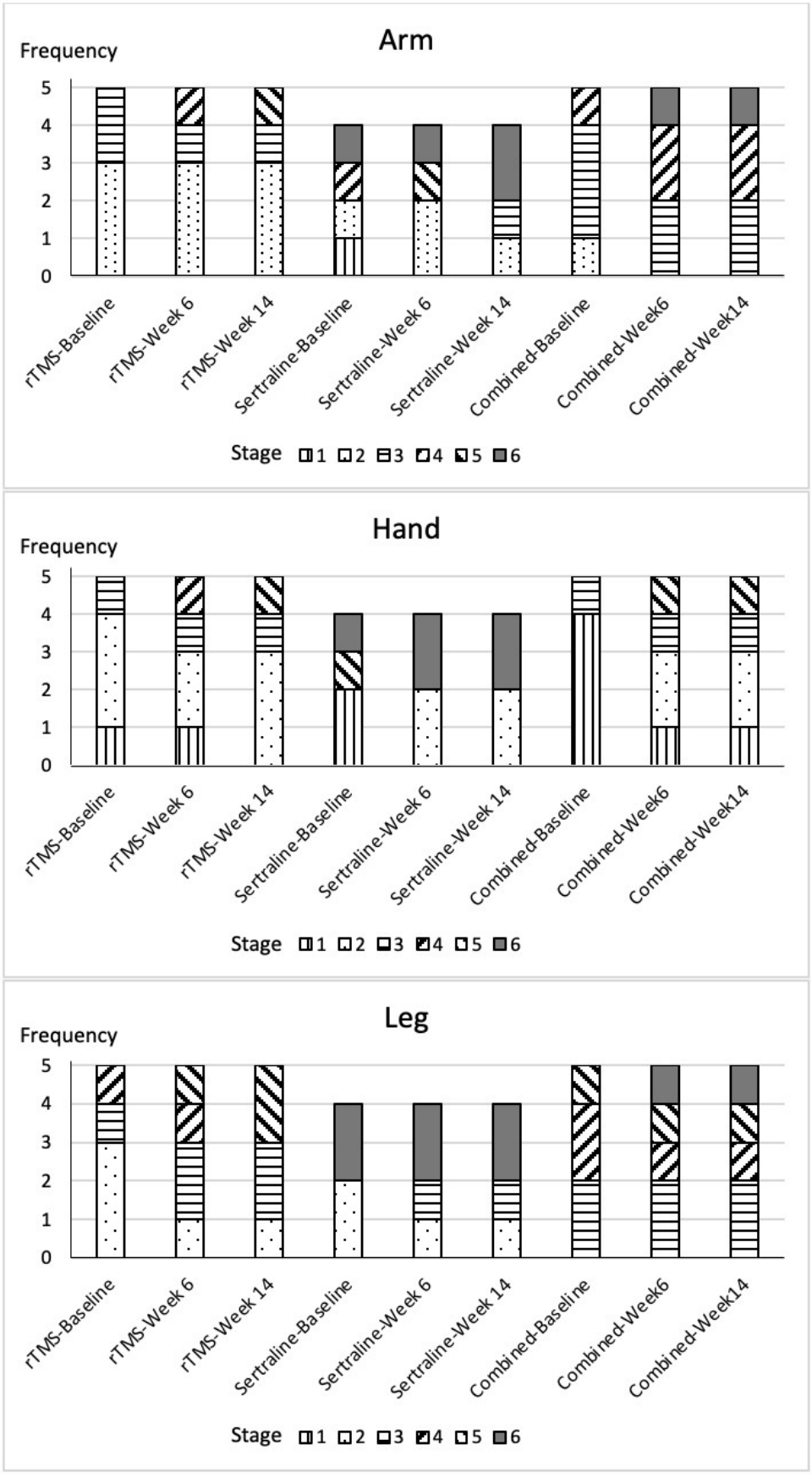

Figure 4. Brunnstrom stages of motor recovery.

In concordance with intention-to-treat analysis, results from per-protocol analysis also showed no statistically significant difference among groups in all outcomes. Reduction in HAM-D score was statistically significant only in the rTMS group.

There were only mild adverse events reported. One subject in the rTMS group developed headache which was resolved after administration of acetaminophen. Two subjects in each group reported dizziness. Severe adverse event such as seizure or hearing impairment was not observed. No statistically significant difference was found among the groups in terms of adverse events.

Discussion

Our current study is the first study published in English language in which compared the antidepressant effects of rTMS with that of sertraline, and also the first research in which investigated effects of rTMS in combination with sertraline. In addition, this is one of studies with a long follow-up period (14 weeks).

In this study, we found that HAM-D score significantly reduced only in the rTMS group. This might be due to unequal baseline HAM-D score among groups although no statistically significant difference in baseline score was found. Subjects in the combined group had milder symptoms whereas those in the rTMS group had more severe symptoms at baseline. Despite less symptom severity at baseline, more percentage of response and remission were found in the combined group, but no statistically significant difference was found among groups.

Sertraline has been widely used in treatment of PSD in Thailand due to patient's tolerability and its inexpensive cost. In this study, we prescribed 50 mg of sertraline daily because a previous study demonstrated no difference in efficacy among dosage of 50, 100 and 200 mg [24] whereas lower dosage was better tolerated than higher dosage. On the contrary, other study found that dosage of 50 mg daily is probably less effective than dosage of 100 mg daily.[25] This might explain failure to observe significant antidepressant effect in our sertraline group.

Previous meta-analyses reported significant improvement in performance on ADL in individuals who received high frequency rTMS compared with control group.[26, 27] Our result showed a significant functional improvement in the rTMS group, but the difference was not statistically significant among groups. Small sample size might result in absence of statistical significance.

Regarding motor recovery, Gu SY, *et al*. demonstrated no statistically significant motor recovery in both rTMS and control groups. There was also no significant difference in the recovery between groups.[18] Chronic stroke period and short duration of follow-up (4 weeks) might explain absence of statistically significant motor recovery in their study. In current study, we conducted investigation in subjects who were in subacute stroke period in which spontaneous neurological recovery was expected but significant motor recovery was not observed in any group. This might also be explained by small sample size.

In accordance with previous studies [16, 17], our subjects in the rTMS and combined groups showed only mild adverse events. There was no discernable difference in adverse events among groups. This finding might indicate safety of high frequency rTMS when used alone or combined with sertraline.

High frequency rTMS alone might be effective in reduction of depressive symptom severity in patients with PSD and its significant antidepressant effects was observed at week 6 after the treatment commencement. It may be considered as a choice in stroke patients with PSD who are unable to tolerate adverse effects of antidepressant medication or who are contraindicated to medication.

One limitation of this study was a small sample size, this might lead to not enough statistical power to demonstrate statistical significance in the outcomes. Therefore, superiority of rTMS in combination with sertraline over rTMS or sertraline alone is still inconclusive.

Conclusion

High frequency rTMS over the left DLPFC might be effective in reduction of depressive symptoms in subacute stroke patients and its effects might not be different from sertraline. Adverse effects of rTMS are not serious. It can be recognized as a choice in treatment of PSD. The benefit of rTMS given in combination with sertraline over rTMS or sertraline alone is still inconclusive. Further investigation in large clinical study is required.

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Conflict of interest

The authors, hereby, declare no conflict of interest.

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