CASE REPORT

LONG-TERM EFFECT OF LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OVER THE UNAFFECTED POSTERIOR PARIETAL CORTEX IN PATIENTS WITH UNILATERAL SPATIAL NEGLECT*

Keiichiro Shindo, Ken Sugiyama, Lu Huabao, Kazunori Nishijima, Takeo Kondo and Shin-Ichi Izumi

From the Department of Physical Medicine and Rehabilitation, Tohoku University Graduate School of Medicine, Sendai, Japan

Objective: To explore long-term effects on unilateral spatial neglect of low-frequency repetitive transcranial magnetic stimulation (rTMS) over the unaffected posterior parietal cortex.

Design: Uncontrolled pilot study.

Subjects: Two chronic-phase patients with left-sided unilateral spatial neglect from cerebral infarction.

Methods: Six rTMS sessions were undertaken for 2 weeks. Each session included 900 stimuli applied over P5 at an intensity of 95% motor thresholds and a frequency of 0.9 Hz. The Behavioural Inattention Test, either the Mini-Mental State Examination or the Revised Hasegawa Dementia Scale, Brunnstrom Recovery Stage, and Barthel Index were evaluated at 2-week intervals until 6 weeks after rTMS sessions. Single-photon emission computed tomography was performed 2 weeks before and after rTMS.

Results: Behavioural Inattention Test scores improved remarkably, especially from 2 to 4 weeks after rTMS sessions. At 6 weeks, Behavioural Inattention Test scores still remained above pre-rTMS levels. Other clinical evaluations as well as single-photon emission computed tomography showed no significant change during the study.

Conclusion: In this small pilot study, low-frequency rTMS over the unaffected posterior parietal cortex decreased unilateral spatial neglect for at least 6 weeks.

Key words: stroke, repetitive transcranial magnetic stimulation, unilateral spatial neglect, Behavioural Inattention Test.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS), a new therapy that affects cortical excitability in a manner depending on stimulation frequency, has been applied to many disorders in psychiatry and neurology. Because low-frequency rTMS reduces excitability in directly stimulated sites as well as in other functionally connected areas (1), stimulation at such frequencies might be expected to improve unilateral spatial neglect (USN) according to the attention-shifting model (2) by correcting the relative hyperactivity of the unaffected hemisphere. In previous studies rTMS was applied over the parietal lobe, the lesion site known to be responsible for USN in healthy subjects (3, 4) and in patients with stroke (4, 6). Brighina et al. (5) reported that left USN in 3 patients with stroke was ameliorated by 7 sessions of 1 Hz subthreshold rTMS over the left posterior parietal cortex (P5). Although they found improvement to be limited until 2 weeks after the rTMS sessions, duration of effect to exceed 2 weeks remained unclear. In addition, they reported changes in USN in terms of 3 visuospatial tasks, but without using standardized instruments such as the Behavioural Inattention Test (BIT) or other cognitive functions.

In this study we explored the long-term effects of low-frequency rTMS over the left posterior parietal cortex in 2 chronic-phase stroke patients with left USN, using well-accepted clinical evaluations including the BIT.

METHODS

Patients
We obtained ethics committee approval at our university hospital for the protocol prior to the study. The 2 patients examined, both right-handed, gave their informed consent for the procedures. Both had right-sided brain damage from cardiogenic brain embolism about 6 months before rTMS (clinical and demographic details are given in Table I). At the beginning of the rTMS study, both patients had severe left hemiparesis and left USN, which was confirmed by the BIT. Left homonymous hemianopsia was demonstrable by ophthalmological examination only in patient B. During the study both patients also underwent physical and occupational therapy 5 times a week without special adaptations or treatment for USN. Both took the same medications.

Procedures
Patients were seated in a comfortable chair in a quiet room with their arms fully supported. The rTMS sessions were carried out on Monday, Wednesday, and Friday for 2 weeks (total, 6 sessions) with biphasic pulses given by a magnetic stimulator (Magstim Rapid System 1000/50,
Table I. Clinical and demographic details of 2 patients with stroke with unilateral spatial neglect. The days given within parenthesis are based on the stroke onset which is set to 0

|                          | Patient A                        | Patient B                        |
|--------------------------|----------------------------------|----------------------------------|
| Age, Sex                 | 59 years, male                   | 61 years, female                 |
| Stroke type              | Cardiogenic brain embolism (right ICA) | Cardiogenic brain embolism (right MCA) |
| Damaged lesions          | Right frontotemporal lesion      | Right temporoparietal lesion     |
| Surgical treatments      | Internal-external decompression (Day 1), cranioplasty (Day 31) | Internal-external decompression (Day 1), cranioplasty (Day 32) |
| Co-morbidity             | Atrial fibrillation              | Atrial fibrillation, hypertension, hyperlipidaemia |
| First rTMS session       | Day 186                          | Day 175                          |
| Clinical evaluations     | BIT-C 68, BIT-B 24, HDS-R 21, BRS I/I/I, BI 35 | BIT-C 35, BIT-B 7, MMSE 23, BRS I/I/I, BI 40, left homonymous hemianopsia |

ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; BIT-C = conventional subtests of the Behavioural Inattention Test; BIT-B = behavioural subtests of the Behavioural Inattention Test; HDS-R = Revised Hasegawa Dementia Scale; MMSE = Mini-Mental State Examination; BRS = Brunnstrom Recovery Stage proximal upper extremity/distal upper extremity/lower extremity; BI = Barthel Index.

RESULTS

Both patients completed the rTMS sessions without adverse symptoms and did not show either epileptiform afterdischarges in the EEG or MEPs from the left APB. BIT scores are shown in Fig. 1. Their BIT scores improved significantly after the rTMS sessions, with peak scores at time 4 in patient A (BIT-C 100, BIT-B 38) and at time 5 in patient B (BIT-C 83, BIT-B 35). In addition, at time 6 BIT scores remained higher than those before the rTMS sessions for both patients.

Other clinical evaluations showed no changes in Brunnstrom Recovery Stage (BRS) or slight change in global cognitive functions (1 point in patient A, 2 points in patient B) during the study. Although BI scores did not change, activities of daily living (ADL) related to USN improved after rTMS sessions in both patients, the best ADL were noted at time 4 in patient A and at time 5 in patient B. For example, difficulty in directing a wheelchair and in transfers between bed and wheelchair decreased. SPECT showed no significant change in cerebral blood flows in either patients between the 2 time points examined.

DISCUSSION

Our results in both patients showed that 0.9 Hz rTMS over the unaffected posterior parietal cortex improved USN according to the BIT. Peak BIT scores were noted at 2 weeks or more after the sessions, and those at 6 weeks still remained better than those at baseline. No significant change in other clinical evaluations was noted during the study.

As for duration of effect of low-frequency rTMS, additive efficacy has been suggested by study of higher numbers of stimulation sessions over several days (1). One session of rTMS induced effects lasting for 15–30 minutes in healthy subjects and for a maximum of 1 week in patients with post-traumatic stress disorder (PTSD) (1). Some studies showed that several daily stimulations with low-frequency rTMS could have affected epilepsy, auditory hallucinations and PTSD for 4–8 weeks (1). Similarly, we found that maximum effects from 6 rTMS sessions over 2 weeks were obtained after 2 weeks or more. The effects persisted in patients with chronic-phase stroke for at least 6 weeks according to the BIT. A possibility, however, existed that rTMS activating a relatively large area could have altered impairments other than USN that affected BIT scores, such as alertness, other forms of inattention, or visuoconstructional and memory deficits. In this study, however, rTMS did not appear to affect global cognitive functions based upon the MMSE or HDS-R.

A difference was noted between patients A and B in that the peak scores appeared later in patient B than in patient A, possibly because of left homonymous hemianopsia in patient B. When left USN and homonymous hemianopsia coexist in patients, more severe left-sided inattention is likely (7). Zihl (8) reported that 60% of their patients with homonymous hemianopsia had impaired visual scanning behaviour.
Additional attention toward the left side induced by rTMS might have resulted from both less left USN and better visual scanning behaviour despite left homonymous hemianopsia in patient B.

In carrying out ADL, both patients required less assistance after the rTMS sessions, and their improvements appeared to be compatible with changes in the BIT scores. Because the improved ADL were related to spatial attention (9), decreased USN might well have induced the improvements. However, BI scores did not change, probably because of limited sensitivity of this index. More sensitive evaluations such as the Functional Independence Measure (FIM™) or the Catherine Berbego Scale (9) might have shown improved scores.

This investigation has obvious limitations characteristic of many pilot studies, such as the small number of subjects, no comparison with sham stimulation, and the possibility of observer bias. In the future, rTMS will need more extensive and better-controlled evaluations in USN, including determinations of optimal timing in stroke rehabilitation treatments.

ACKNOWLEDGEMENT

This research was supported by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Science, Sports and Culture of Japan (no. 15300191).

REFERENCES

1. Hoffman RE, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. Am J Psychiatry 2002; 159: 1093–1102.
2. Kinsbourne M. Mechanisms of unilateral neglect. In: Jeannerod M, ed. Neurophysiological and neuropsychological aspects of spatial neglect. Amsterdam: North-Holland; 1987, pp. 69–86.
3. Sack AT, Hubl D, Prvulovic D, Formisano E, Jandl M, Zanella FE, et al. The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. Brain Res Cogn Brain Res 2002; 13: 85–93.
4. Pierro B, Brighina F, Olivieri M, Piazza A, La Bua V, Buffa D, et al. Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. Neuroreport 2000; 11: 1519–1521.
5. Brighina F, Bisiach E, Olivieri M, Piazza A, La Bua V, Daniele O, et al. 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralateral visuospatial neglect in humans. Neurosci Lett 2003; 336: 131–133.
6. Olivieri M, Bisiach E, Brighina F, Piazza A, La Bua V, Buffa D, et al. rTMS of the unaffected hemisphere transiently reduces contralateral visuospatial hemineglect. Neurology 2001; 57: 1338–1340.
7. Cassidy TP, Bruce DW, Lewis S, Gray CS. The association of visual field deficits and visuo-spatial neglect in acute right-hemisphere stroke patients. Age Ageing 1999; 28: 257–260.
8. Zihl J. Visual scanning behavior in patients with homonymous hemianopsia. Neuropsychologia 1995; 33: 287–303.
9. Azouvi P, Olivier S, de Montety G, Samuel C, Louis-Dreyfus A, Tesio L. Behavioral assessment of unilateral neglect: study of the psychometric properties of the Catherine Berbego Scale. Arch Phys Med Rehabil 2003; 84: 51–57.