Clinical Neurophysiology 118 (2007) 702–708

www.elsevier.com/locate/clinph

# Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations

Eun Yeon Joo [a,c], Sun Jung Han [a], So-Hee Chung [b], Jae-Wook Cho [a], Dae Won Seo [a], Seung Bong Hong [a,*]

[a] *Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-Dong, Gangnam-gu, 135-710 Seoul, South Korea*

[b] *Clinical Trial Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-Dong, Gangnam-gu, 135-710 Seoul, South Korea*

[c] *Department of Neurology, College of Medicine, Ewha Womans University, Seoul, South Korea*

Accepted 15 November 2006

**Abstract**

*Objective:* To evaluate the antiepileptic effect of low-frequency rTMS (repetitive transcranial magnetic stimulation) in the patients with intractable epilepsy.

*Methods:* We enrolled 35 patients with localization-related epilepsy who had experienced at least one complex partial seizure or a secondarily generalized seizure per week on a constant antiepileptic drug regimen over an 8-week period. rTMS was administered using a *Rapid*$^2$ magnetic stimulator with an air-cooled coil at 0.5 Hz for 5 consecutive days at 100% of rMT (resting motor threshold). Patients were divided into a focal stimulation group with a localized epileptic focus, or a non-focal stimulation group with a non-localized or multifocal epileptic focus. These two groups were then randomly subdivided into four subgroups depending on the total number of stimulations administered, i.e., 3000 pulse and 1500 pulse subgroups. Weekly seizure frequencies were determined for 8 weeks before and after rTMS. To compare the number of interictal spikes before and after rTMS, EEG was recorded twice before (1st day) and after rTMS (5th day).

*Results:* Mean weekly seizure frequency was non-significantly decreased after rTMS (8.4 → 6.8/week, −13.9%). Longer stimulation subgroups (3000 pulses, −23.0%) tended to have fewer seizures than shorter stimulation subgroups (1500 pulses, −3.0%), without statistical significance. TMS stimulation site and structural brain lesions did not influence seizure outcome. However, interictal spikes significantly decreased (−54.9%, $P = 0.012$) after rTMS and they totally disappeared in 6 patients (17.1%, 6/35).

*Conclusions:* Low-frequency rTMS reduced interictal spikes, but its effect on seizure outcome was not significant. Focal stimulation for a longer duration tended to further reduce seizure frequency.

*Significance:* These findings may help clinicians to further investigate the therapeutic potential of the rTMS for patients with intractable epilepsy.



*Keywords:* Transcranial magnetic stimulation; Epilepsy; Seizure outcome; Interictal spike

## 1. Introduction

Transcranial magnetic stimulation (TMS) has become an important diagnostic tool for evaluating the degree of cortical excitability in the human brain. Repetitive TMS (rTMS) can be used to modulate cortical excitability, and the potential therapeutic role of rTMS in epilepsy is being increasingly recognized. Low-frequency rTMS of the primary motor cortex produces a transient reduction in the excitability of neurons generating motor evoked potentials (MEPs) (Tassinari et al., 2003). Long-term depression, a phenomenon associated with synaptic plasticity, which can be induced by rTMS, might be part of the underlying

* Corresponding author. Tel.: +82 2 3410 3592; fax: +82 2 3410 0052.
*E-mail address:* sbhong@smc.samsung.co.kr (S.B. Hong).

1388-2457/$32.00 
doi:10.1016/j.clinph.2006.11.008

mechanism. In contrast to high-frequency rTMS, which can produce subsequent cortical excitation and seizure induction (Wassermann, 1998), low-frequency rTMS is neither epileptogenic nor painful. Low-frequency rTMS prolonged the latency of the development of pentylenetetrazol-induced seizures in rats, which provided a rationale for using low-frequency TMS to treat patients with epilepsy (Akamatsu et al., 2001). In an open pilot study, the antiepileptic effect of 0.33 Hz rTMS for 5 consecutive days was investigated in nine patients with focal epilepsy (Tergau et al., 1999). Each day, two trains of 500 pulses at 100% of resting motor threshold were delivered using a round coil. During the post-intervention period, seizure frequency was found to be significantly reduced as compared with the pre-intervention period. After this report, a number of rTMS trials were conducted. A recent controlled study, using 1 Hz rTMS for 15 min twice daily for one week at 120% of motor threshold (MT), showed a trend of short-term seizure decrease mainly in patients with neocortical rather than mesial temporal foci (Theodore et al., 2002). Different rTMS frequencies (0.33 vs. 1 Hz) and intensities (100% vs. 120%) might produce different results. Two previous studies suggested that low-frequency (less than 1 Hz) rTMS reduced interictal EEG activity (Menkes and Gruenthal, 2000; Steinhoff et al., 1993), but the effects of rTMS were reported to be transient and mild on clinical outcome in epileptic patients (Theodore et al., 2002). A case report showed 70% seizure reduction by 0.5 Hz low-frequency rTMS in a patient with intractable partial seizures due to focal cortical dysplasia in the parietal region (Menkes and Gruenthal, 2000). And, a recent open pilot study involving four patients with epilepsy due to cortical dysplasia used 0.5 Hz rTMS consisting of 100 pulses at 90% of motor threshold, and showed that rTMS reduced seizure frequency in patients with a single epileptic focus, but not in patients with multiple foci (Daniele et al., 2003). However, most of these studies were confined to a small number of patients treated with rTMS at varying stimulus rates, intensity, and durations. Moreover, neither adequate stimulation parameters nor factors for predicting the efficacy of rTMS on epilepsy have been fully established. In this study we adopted the 0.5 Hz rTMS protocol for treating intractable epilepsy, and then investigated the efficacy of low-frequency rTMS on seizure frequency on the number of interictal epileptiform discharges, and on cortical excitability according to stimulation duration (3000 pulses vs. 1500 pulses a day) and site (focal vs. non-focal stimulation).

## 2. Methods

### 2.1. Patients

We enrolled 35 patients (18 males) with localization-related epilepsy who had suffered from uncontrolled partial and secondarily generalized seizures. Patients were recruited from the epilepsy clinic at Samsung Medical Center, Seoul, Korea. Inclusion criteria were: (i) at least one complex partial (CPS) or secondarily generalized seizure per week on a constant antiepileptic drug (AED) regimen, (ii) an epilepsy history of over 2 years, (iii) an age of more than 18 years, (iv) the same AED regimen over a 8-week baseline period, (v) no history of neuroleptic medication except AED, and (vi) no history of neurological or psychiatric disease.

Daily seizures were recorded on a seizure diary from 8 weeks before rTMS until 8 weeks after rTMS treatment. Number of seizures was counted. Seizure reduction rate was calculated by [(mean weekly seizure number, MWSN, during 8 weeks before rTMS − MWSN during 8 weeks after rTMS)/MWSN during 8 weeks before rTMS] × 100(%).

### 2.2. EEG recordings

To compare numbers of interictal spikes of pre- and post-rTMS treatment, baseline EEG was performed on the 1st day of rTMS treatment before rTMS was started and a follow-up EEG was done on the 5th day of treatment after the last session of rTMS (Fig. 1). Patients were invited to lie down on a bed in a dark sound-attenuated room. The 64-channel EEG (according to the international 10-10 system) was recorded during both awake and sleep periods. EEG recording was continued until 15 min waking and 15 min sleep EEGs were obtained using a digital EEG system (Neuroscan, USA). The band pass filter setting was 0.5–70 Hz. Sleep stage of sleep EEG was either stage 1 or 2 according to the standard criteria (Rechtshaffen and Kales, 1968). Proportions of stage 1 and 2 sleep were not significantly different among 4 subgroups. The number of interictal spikes on the EEG was counted for 15 min waking and 15 min sleep EEGs. Interictal spikes were defined by distinctive and apiculate waveforms (spikes/sharp waves) or complexes with appropriate field distribution and following slow wave, which were distinguished from sharply contoured waves of normal or abnormal background activity. The number of spikes was counted by one well-trained, long-experienced epileptologist (Hong

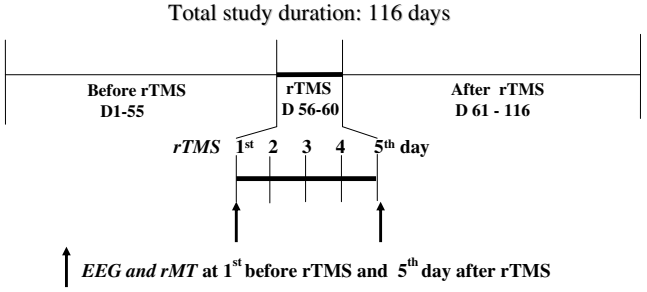


Fig. 1. Time schedule for repetitive transcranial magnetic stimulation (rTMS), EEG recording, and resting motor threshold (rMT) measurement. Patients were instructed to keep a seizure diary from 8 weeks prior to rTMS treatment until 8 weeks after rTMS. Resting motor threshold was measured twice before and after 5-day rTMS treatment. EEG was also recorded twice, just before and after 5-day rTMS treatment.

SB), who was blinded to the information of the patient, timing of EEG recording, duration or location of rTMS.

### 2.3. TMS procedure

We used a Rapid$^2$ magnetic stimulator (Magstim, UK), which produces a biphasic pulse, and a forced air-cooled circular (90 mm diameter winding) or double 70 mm configuration coil. Resting motor threshold (rMT) was defined as the minimum percentage of stimulator output that induced a MEP of $\geqslant 50$ μV in at least 5 of 10 trials. rMT was measured in right and left motor cortices, respectively. Surface electromyography (EMG) was recorded from the right or left flexor digitorum indicis (FDI) muscle. An auditory feedback EMG signal was produced to ensure complete voluntary relaxation of the target muscle. Placement of the coil over the motor cortex was performed by finding and marking a scalp site that was optimal in terms of producing MEPs in FDI muscle.

The location of epileptic focus was determined by the results of ictal/interictal EEG in conjunction with brain MRI, ictal SPECT, $^{18}$F-fluorodeoxy glucose positron emission tomography, and SISCOM (subtraction ictal SPECT co-registered to MRI) (Lee et al., 2000). A coil was positioned over the area of epileptic focus, which was targeted using a Frameless image guidance system, *Brainsight* (Focal stimulation, the **F** group). The central vertex (10-20 international system) was targeted in patients with multifocal or non-localized epilepsy (Non-Focal stimulation, the **NF** group). Patients were kept on an unchanged AED regimen over the 8 weeks pre- and post-rTMS periods. Daily seizures were recorded on a seizure diary from 8 weeks pre- and to 8 weeks post-rTMS treatment. Number of seizures was counted and seizure reduction rate was calculated. To compare numbers of interictal spikes of pre- and post-rTMS periods, baseline EEG was performed pre-rTMS on the 1st day of treatment and a follow-up EEG was done on the 5th day of treatment post-rTMS (Fig. 1).

### 2.4. rTMS protocol

rTMS was administered at 0.5 Hz once a day for a consecutive 5 days at 100% of rMT. Patients in the **F** and **NF** groups were randomly divided into 3000 pulse (stimulation duration: 100 min a day) and 1500 pulse subgroups (50 min a day). Stimulation intensity was determined as 100% of rMT in the hemisphere ipsilateral to the epileptic focus in the F group and that in the dominant hemisphere in the NF group. During rTMS sessions patients were comfortably seated in an armchair and a custom-built apparatus held the coil on a rigid arm to target an ictal focus or the central vertex. Coil position was monitored visually throughout stimulation sessions. The Institutional Review Board of Samsung Medical Center approved the study protocol and the written consent form used.

## 3. Results

### 3.1. Patients

Mean age of the patients was 25 years (range 18–46) and the mean duration of epilepsy was 8 years (range 2–21). Mean frequency of CPS or secondarily generalized seizure was 9.1 per week (range 1–25). All subjects were right-handed. The mean number of AEDs taken throughout the 17-week study period was $3.6 \pm 1.4$ (range 2–7). Non-focal stimulation was performed in 17 patients (the **NF** group) over the central vertex (Cz in the international 10-20 system). Fifteen of them (15/17, 88.2%) did not show structural abnormalities on their MRI scans. Of the two that did, one had encephalomalacia in left and right temporo-occipital areas and the other showed bilateral hippocampal sclerosis. Eight patients (8/17, 47%) had multifocal (more than two) epileptic foci and in the remaining 9 (53%) we failed to localize the epileptic focus (non-localized).

Focal stimulation over the epileptic focus was performed in 18 patients (the **F** group). Seven of the 18 (38.8%) had normal MRI findings, and targets for stimulation were determined by ictal EEG or the distribution of interictal spikes. Six patients had structural lesions, such as, encephalomalacia, cortical dysplasia, and cavernous malformations, which corresponded to epileptic foci (12 patients over the right or left temporal lobe, 3 over the left frontal lobe, and 3 over the right parietal lobe).

According to a randomization code, patients were assigned to the following subgroups; 9 to the **NF**-3000 subgroup, 8 to **NF**-1500, 8 to **F**-1500, and 10 to **F**-3000. All patients underwent rTMS for 5 days without serious side effects. Five patients complained of a mild and transient headache during and immediately after rTMS.

### 3.2. rTMS effect on seizure frequency

When the baseline 8-week and post-stimulation 8-week periods were compared in all patients, mean numbers of CPS or secondarily generalized seizures per week were found to be non-significantly decreased after rTMS treatment ($N = 35$, $8.4 \pm 9.8$/week $\rightarrow 6.8 \pm 9.0$/week, $-13.91\%$, $P = 0.087$).

Seizure frequency was not significantly decreased after rTMS treatment in the **NF** ($N = 17$, $9.9 \pm 10.1$/week $\rightarrow 7.2 \pm 4.8$/week ($-12.0\%$), $P = 0.152$) or **F** groups ($N = 18$, $7.0 \pm 9.6$/week $\rightarrow 6.4 \pm 9.0$/week ($-15.6\%$), $P = 0.153$). TMS stimulation sites did not produce different results in terms of seizure outcome ($-12.0 \pm 25.6\%$ in the **NF** group vs. $-15.6 \pm 40.6\%$ in **F** group, student $t$-test, $P = 0.763$).

Changes in seizure frequency were not significantly different for longer and shorter stimulation periods. However, a longer rTMS stimulation period (3000 pulses a day, $N = 19$) ($8.6 \pm 10.6$/week $\rightarrow 6.1 \pm 6.5$/week ($-23.0\%$), paired $t$-test, $P = 0.198$) tended to reduce seizure frequency

more so than a shorter stimulation (1500 pulses a day, $N = 16$) ($8.2 \pm 9.1$/week $\rightarrow$ $7.6 \pm 8.0$/week ($-3.0\%$), $P = 0.149$), but without statistical significance (Student's $t$-test, $P = 0.633$).

In subgroup analysis, the seizure reduction rate after rTMS was significantly greater in 3000 pulses subgroup ($30.6 \pm 43.1\%$) than in 1500 pulses subgroup ($-3.1 \pm 34.6\%$) in **F** group (Mann–Whitney test, $P = 0.043$) whereas no difference of seizure reduction rate was found between 3000 and 1500 pulses subgroups in **NF** group ($P = 0.673$).

Seizure reduction rates after rTMS in four subgroups are listed and depicted in Table 1 and Fig. 2.

Thirty percent (3/10 patients) of the **F**-3000 subgroup experienced a $\geqslant 50\%$ seizure reduction (66.3–90.0%), whereas one patient in **F**-1500 ($N = 8$) and one in **NF**-3000 ($N = 9$) experienced seizure reductions of 61.3% and 71.6%, respectively. In the **NF**-1500 subgroup ($N = 8$), no patient reported more than a 50% seizure reduction after rTMS treatment (see Table 1).

Mean weekly seizure frequency before rTMS treatment was not significantly different between patients with normal MRI findings ($N = 22$, $10.4 \pm 11.3$/week) and those with structural abnormalities on MRI ($N = 13$, $4.9 \pm 5.2$/week, student $t$-test, $P = 0.113$). Seizure frequency changes after rTMS treatment were not significant in these two MRI groups ($10.4 \pm 11.3$/week $\rightarrow$ $8.1 \pm 7.8$/week,$-21.8\%$, paired $t$-test, $P = 0.119$ in the normal MRI group vs. $4.9 \pm 5.2$/week $\rightarrow$ $4.5 \pm 5.4$/week, $-8.4\%$, $P = 0.351$ in the abnormal MRI group) and seizure frequency changes after rTMS treatment in these two groups were not significantly different (student $t$-test, $P = 0.325$).

### 3.3. The effect of rTMS on interictal epileptiform discharges

rTMS treatment significantly reduced the number of interictal spikes ($253.2 \pm 397.0$/30 min $\rightarrow$ $102.4 \pm 192.6$/30 min, $54.9 \pm 42.2\%$ reduction, paired $t$-test, $P = 0.012$). Notably, interictal spikes were totally abolished in 6 patients (6/35, 17.1%) after rTMS treatment.

However, reduction rates of interictal spikes after rTMS were not different between **F** vs. **NF** or 1500 pulses vs. 3000 pulses groups ($56.6 \pm 33.8\%$ in the **NF** group vs. $57.0 \pm 39.5\%$ in **F** group, Student's $t$-test, $P = 0.961$; $51.0 \pm 38.2\%$ in the 1500 group vs. $60.0 \pm 35.5\%$ in 3000 group, $P = 0.496$). The reduction rates of interictal spikes were not different among the 4 subgroups too ($46.2 \pm 43.0\%$ in the NF-1500 group vs. $65.8 \pm 21.5\%$ in NF-3000 group vs. $53.8 \pm 35.3\%$ in F-1500 group vs. $59.9 \pm 44.3\%$ in F-3000 group, Kruskal–Wallis test, $P = 0.856$).

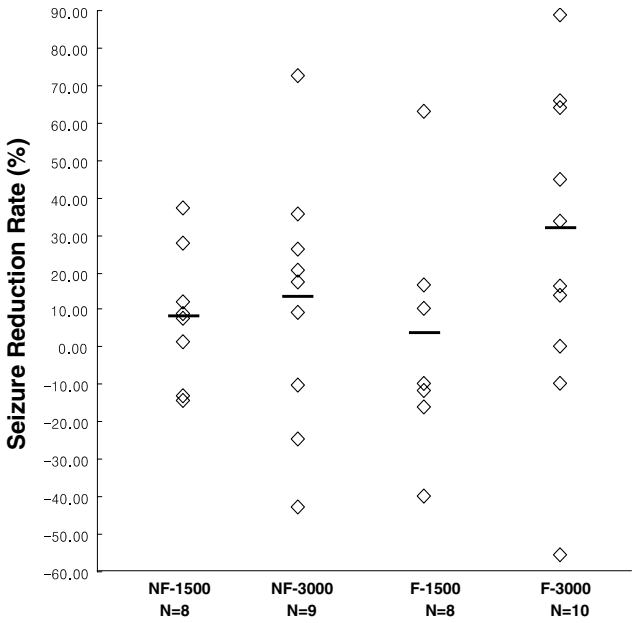


Fig. 2. Seizure reduction rates after 5-day rTMS treatment in patients of four subgroups (NF-1500, NF-3000, F-1500 and F-3000). Seizure reduction rates were depicted on $Y$-axis in each subgroup ($X$-axis). Seizure reduction rate was calculated by [(mean weekly seizure number (MWSN) during 8 weeks before rTMS − MWSN during 8 weeks after rTMS)/MWSN during 8 weeks before rTMS] × 100(%). Horizontal bars indicate the mean seizure reduction rate in each subgroup.

### 3.4. Effect of rTMS on resting motor threshold

In the **F** group at baseline ($N = 18$), the intensity of rMT in the ipsilateral hemisphere (IH) to the epileptic focus was similar to that in the contralateral hemisphere (CH) ($78.0 \pm 15.8\%$ in IH vs. $77.5 \pm 17.8\%$ in CH, Student's $t$-test, $P = 0.805$). After 5-days of rTMS treatment, the

Table 1
Seizure frequencies according to stimulation site and duration

| Site | Pulses | Mean seizure number per week | | | | The number of patients with $\geqslant 50\%$ seizure reduction |
|---|---|---|---|---|---|---|
| | | Before# | After# | SRR[a] (%) | P* | |
| **NF** | 1500 ($N = 8$) | 8.3(4.5) | 7.3(4.0) | 9.1 | 0.126 | 0 |
| | 3000 ($N = 9$) | 11.3(13.5) | 7.1(5.6) | 14.7 | 0.242 | 1 |
| **F** | 1500 ($N = 8$) | 8.1(12.6) | 7.8(11.1) | −3.1 | 0.767 | 1 |
| | 3000 ($N = 10$) | 6.0(7.6) | 5.2(8.0) | 30.6 | 0.059 | 3 |

**NF**, non-focal; **F**, focal stimulation. Before# and After# indicate the mean weekly seizure number during the 8 weeks periods before and after 5-day rTMS treatment.

[a] SRR: Seizure Reduction Rate = [(Before# − After#)/Before#] × 100(%).

* Significant at the $P$-value < 0.05, Wilcoxon signed ranks test.

intensity of rMT was not significantly changed in IH ($78.0 \pm 15.8\% \rightarrow 76.5 \pm 17.8\%$, paired $t$-test, $P = 0.109$) or in CH ($77.5 \pm 17.8\% \rightarrow 77.6 \pm 16.6\%$, $P = 0.115$).

In the **NF** group ($N = 17$), the rMT intensities in both dominant ($80.5 \pm 13.5\% \rightarrow 80.2 \pm 14.1\%$, $P = 0.951$) and non-dominant hemispheres ($79.4 \pm 11.3\% \rightarrow 80.1 \pm 9.8\%$, $P = 0.875$) were unaltered by 5 days rTMS treatment.

No statistically significant difference in rMT was observed between the F and NF groups before (student $t$-test, $P = 0.624$) or after rTMS ($P = 0.532$).

## 4. Discussion

The aim of this study was to investigate the efficacy of low-frequency rTMS on seizure frequency, the number of interictal epileptiform discharges, and cortical excitability according to stimulation duration and stimulation site using a 0.5 Hz rTMS protocol. Recent studies have produced favorable seizure control outcomes using 0.5 Hz rTMS protocols. Focal stimulation based on one session of 0.5 Hz (600 pulses) targeting cortical malformations significantly decreased the number of interictal spikes on EEG recorded at 15th (−46.4%) and 30th days (−42.1%), after rTMS treatment (Fregni et al., 2005). Seizure frequency was also significantly reduced from 4.6/week (baseline) to 2.2/week (at 15 days of post-treatment) and 2.0/week (30 days), showing that the antiepileptic effect was sustained at least for 1 month after treatment. Another case study in a patient with epilepsia partialis continua showed that the therapeutic effects of low-frequency 0.5 Hz rTMS lasted for approximately 2 months (Misawa et al., 2005). However, these studies were confined to a small number of patients (one of 8 and the other of 1 patient) and all patients had an epileptic focus of cortical dysplasia. Moreover, antiepileptic effect of TMS was the highest when stimulation was targeted on the cortical malformation because magnetic field reaches the first cortical layer of the stimulated area (Oliveri et al., 2005).

Our results show that seizure outcomes for focal stimulation targeting epileptic foci and non-focal stimulation (**F** vs. **NF**) were not different. Focal rTMS reduced the mean frequency of CPS or secondarily GTC by 15.6%, whereas **NF** stimulation decreased them by 12.0%. Previous studies have reported that the antiepileptic effect of rTMS is better in TLE patients with a neocortical lesion than in those with mesial temporal sclerosis (Theodore et al., 2002). Patients with epilepsy due to cortical dysplasia have also been reported to be best candidates for therapeutic rTMS (Misawa et al., 2005; Rossi et al., 2004). Direct stimulation focally targeting lesions successfully suppressed intractable seizures (Daniele et al., 2003; Misawa et al., 2005; Oliveri et al., 2005; Rossi et al., 2004; Theodore et al., 2002). In our study, most **NF** group patients (15/17, 88%) had no structural lesion. Seven in the **NF** group showed non-localized ictal EEG onset and the remaining 10 had multifocal epileptic foci. In the **F** group ($N = 18$), five patients had unilateral or bilateral hippocampal sclerosis and the other 13 showed extensive encephalomalacia over more than two lobes. Our results suggest that the antiepileptic effects of rTMS are not significantly different for focal and non-focal stimulation. However, the lack of cortical malformation and inhomogeneous epileptogenic lesions in our cohort may explain the non-significant difference found between seizure outcomes after rTMS treatment in the **F** and **NF** groups.

Our study shows that rTMS of longer duration (3000 pulses a day) tended to decrease seizure frequency more so than rTMS of shorter duration (1500 pulses). Three thousand pulses of rTMS per day reduced seizures by 23.0%, whereas 1500 pulses of rTMS per day decreased seizures by 3.0%. As far as we know, no study has been undertaken to investigate the effect of stimulation duration on seizure outcome. In depressive patients, long-term maintenance therapy with rTMS produced favorable antidepressant effects (O'Reardon et al., 2005). Stimulation was performed over the left prefrontal cortex at a frequency of 10 Hz (2000 pulses per session), for periods ranging from 6 months to 6 years. It was concluded that long-term rTMS is safe and that it modulates neural function without up-regulating the inflammatory mediators known to be involved in neurodegenerative disorders, according to animal studies (Okada et al., 2002).

However, in epilepsy, stimulation durations have shown variable effects on seizure outcome. For daily stimulation, one study reported a significant reduction in refractory seizures after a consecutive 5 days of rTMS (1000 pulses a day) (Tergau et al., 1999), but another study failed to find a definite decrease in seizure frequency after a consecutive 7 days of rTMS (900 pulses twice a day) (Theodore et al., 2002). Intermittent stimulation (twice a week) was reported to cause mean daily seizure reductions in 3 patients but to increase the seizures in 2 patients after 12 weeks of rTMS treatment (Brasil-Neto et al., 2004). On the other hand, rTMS in 4 patients with single cortical dysplasia showed a slight reduction in seizure frequencies (Daniele et al., 2003).

Although it did not reach statistical significance, our focal stimulation group that received 3000 pulses per session ($N = 10$) showed the highest level of seizure reduction (−30.3%) and three patients of this group experienced more than a 50% seizure reduction. The highest reduction rate observed after rTMS was 90.0%, which occurred in a patient with right hemiatrophy and encephalomalacia over the right temporo-occipital region and schizencephaly in the right hemisphere. During long-term video-EEG monitoring, the seizure focus in this female patient was localized to the right centro-temporal area by ictal EEG onset (C4, T8) and SISCOM (subtraction ictal-interictal SPECT co-registered to MRI). Using a *Brainsight* (frameless image guidance system), rTMS was precisely targeted to the epileptic focus in this patient.

rTMS significantly reduced the number of interictal spikes ($-54.9 \pm 42.2\%$, paired $t$-test, $P = 0.012$). Moreover, in 6 patients (17.1%, 6/35), interictal spikes were

totally abolished after 5 days of rTMS treatment. Several studies have reported the suppressive effect that low-frequency rTMS has on interictal spikes (Fregni et al., 2005; Menkes and Gruenthal, 2000; Rossi et al., 2004; Tergau et al., 1999). A recent case report found that low-frequency rTMS delivered over the vertex reduced epileptic discharges arising from the occipital cortex (Mecarelli et al., 2006). Moreover, the suppression of epileptic activity in different remote areas by TMS (Civardi et al., 2001; Hamer et al., 2005) may explain interictal spike reductions in our **NF** patients with vertex stimulation.

Motor thresholds reflect membrane excitability and the balance between inhibitory and excitatory inputs from local circuits (Hallett, 2000). The present study shows a relatively high rMT in enrolled patients (mean $78.0 \pm 15.8\%$ in the hemisphere ipsilateral to the epileptic focus vs. $77.5 \pm 17.8\%$ in the contralateral hemisphere in the focal stimulation group, and $80.5 \pm 13.5\%$ in non-focal stimulation). The decreased cortical excitabilities of our patients may be related to their antiepileptic medications. All of our patients were taking AEDs, such as, sodium channel blockers (carbamazepine, phenytoin) or lamotrigine, which are known to increase MT values (Chen et al., 1997; Ziemann et al., 1996). Although no significant changes in rMT were observed at one day or five days after low-frequency rTMS in the present study, previous studies have found reduction in MEP size (Gerschlager et al., 2001), task-related EEG power and EEG-EMG coherence (Chen et al., 2003) after sub-threshold low-frequency rTMS administration to the premotor cortex, which suggests ipsilateral motor cortex inhibition.

The small number of patients in the subgroup analysis limited our study in terms of determining the effects of stimulation site and duration.

## 5. Conclusion

After low-frequency rTMS treatment for 5-days, CPS frequency with/without secondarily generalized seizures was reduced by 13.9% (non-significant). Our findings suggest that epileptic patients that receive focal stimulation to the epileptic focus may have a better therapeutic outcome than those that receive non-focal stimulation, and that the administration of more pulse per one rTMS session may be an effective way of controlling intractable seizures, although these findings failed to achieve significance. However, interictal spikes were significantly reduced by rTMS, which provides supporting evidence that rTMS offers a potential alternative treatment modality for intractable epilepsy.

## Acknowledgements

This study was supported by a grant (No. A050462) of the Good Health R&D Project, Ministry of Health & Welfare, Republic of Korea, and by a grant (M103KV010016-06K2201-01610) from Brain Research Center of the 21st Century Frontier Research Program funded by the Ministry of Science and Technology of the Republic of Korea, and by the Samsung Medical Center Clinical Research Development Program grant, #CRS105-18-1.

## References

Akamatsu N, Fueta Y, Endo Y, Matsunaga K, Uozumi T, Tsuji S. Decreased susceptibility to pentylenetetrazol-induced seizures after low-frequency transcranial magnetic stimulation in rats. Neurosci Lett 2001;310:153–6.

Brasil-Neto JP, de Arujo DP, Teixeira WA, Araujo VP, Boechat-Barros R. Experimental therapy of epilepsy with transcranial magnetic stimulation: lack of additional benefit with prolonged treatment. Arq Neuropsiquiatr 2004;62:21–5.

Chen R, Samii A, Canos M, Wassermann EM, Hallett M. Effects of phenytoin on cortical excitability in humans. Neurology 1997;49:881–3.

Chen WH, Mima T, Siebner HR, Oga T, Hara H, Satow T, et al. Low-frequency rTMS over lateral premotor cortex induces lasting changes in regional activation and functional coupling of cortical motor areas. Clin Neurophysiol 2003;114:1628–37.

Civardi C, Cantello R, Asselman P, Rothwell JC. Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. Neuroimage 2001;14:1444–53.

Daniele O, Brighina F, Piazza A, Giglia G, Scalia S, Fierro B. Low-frequency transcranial magnetic stimulation in patients with cortical dysplasia – a preliminary study. J Neurol 2003;250:761–2.

Fregni F, Thome-Souza S, Bermpohl F, Marcolin MA, Herzog A, Pascual-Leone A, et al. Antiepileptic effects of repetitive transcranial magnetic stimulation in patients with cortical malformations: an EEG and clinical study. Stereotact Funct Neurosurg 2005;83:57–62.

Gerschlager W, Siebner HR, Rothwell JC. Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 2001;57:449–55.

Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000;406:147–50.

Hamer HM, Reis J, Mueller HH, Knake S, Overhof M, Oertel WH, et al. Motor cortex excitability in focal epilepsies not including the primary motor area – a TMS study. Brain 2005;128:811–8.

Lee HW, Hong SB, Tae WS. Opposite ictal perfusion patterns of subtracted SPECT. Hyperperfusion and hypoperfusion. Brain 2000;123:2150–9.

Mecarelli O, Gregori B, Gilio F, Conte A, Frasca V, Accornero N, et al. Effects of repetitive transcranial magnetic stimulation in a patient with fixation-off sensitivity. Exp Brain Res 2006;173:180–4.

Menkes DL, Gruenthal M. Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. Epilepsia 2000;41:240–2.

Misawa S, Kuwabara S, Shibuya K, Mamada K, Hattori T. Low-frequency transcranial magnetic stimulation for epilepsia partialis continua due to cortical dysplasia. J Neurol Sci 2005;234:37–9.

Okada K, Matsunaga K, Yuhi T, Kuroda E, Yamashita U, Tsuji S. The long-term high-frequency repetitive transcranial magnetic stimulation does not induce mRNA expression of inflammatory mediators in the rat central nervous system. Brain Res 2002;957:37–41.

Oliveri M, Koch G, Torriero S, Caltagirone C. Increased facilitation of the primary motor cortex following 1 Hz repetitive transcranial magnetic stimulation of the contralateral cerebellum in normal humans. Neurosci Lett 2005;376:188–93.

O'Reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimiento PC. Long-term maintenance therapy for major depressive disorder with rTMS. J Clin Psychiatry 2005;66:1524–8.

Rechtshaffen A, Kales A. A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects. UCLA, Brain Information Service/Brain Research Institute, Los Angeles, 1968.

Rossi S, Ulivelli M, Bartalini S, Galli R, Passero S, Battistini N, et al. Reduction of cortical myoclonus-related epileptic activity following slow-frequency rTMS. Neuroreport 2004;15:293–6.

Steinhoff BJ, Stodieck SR, Zivcec Z, Schreiner R, von Maffei C, Plendl H, et al. Transcranial magnetic stimulation (TMS) of the brain in patients with mesiotemporal epileptic foci. Clin Electroencephalogr 1993;24:1–5.

Tassinari CA, Cincotta M, Zaccara G, Michelucci R. Transcranial magnetic stimulation and epilepsy. Clin Neurophysiol 2003;114:777–98.

Tergau F, Naumann U, Paulus W, Steinhoff BJ. Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. Lancet 1999;353:2209.

Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, et al. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. Neurology 2002;59:560–2.

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, 5–7 June 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16.

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 1996;40:367–78.