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EXPERIMENTAL THERAPY OF EPILEPSY WITH TRANSCRANIAL MAGNETIC STIMULATION

Lack of additional benefit with prolonged treatment

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ABSTRACT - *Objective:* To investigate the effect of three months of low-frequency repetitive transcranial magnetic stimulation (rTMS) treatment in intractable epilepsy. Methods: Five patients (four males, one female; ages 6 to 50 years), were enrolled in the study; their epilepsy could not be controlled by medical treatment and surgery was not indicated. rTMS was performed twice a week for three months; patients kept records of seizure frequency for an equal period of time before, during, and after rTMS sessions. rTMS was delivered to the vertex with a round coil, at an intensity 5 % below motor threshold. During rTMS sessions, 100 stimuli (five series of 20 stimuli, with one-minute intervals between series) were delivered at a frequency of 0.3 Hz. *Results*: Mean daily number of seizures (MDNS) decreased in three patients and increased in two during rTMS- one of these was treated for only one month; the best result was achieved in a patient with focal cortical dysplasia (reduction of 43.09 % in MDNS). In the whole patient group, there was a significant ($p<0.01$) decrease in MDNS of 22.8 %. *Conclusions*: Although prolonged rTMS treatment is safe and moderately decreases MDNS in a group of patients with intractable epilepsy, individual patient responses were mostly subtle and clinical relevance of this method is probably low. Our data suggest, however, that patients with focal cortical lesions may indeed benefit from this novel treatment. Further studies should concentrate on that patient subgroup.

KEY WORDS: transcranial magnetic stimulation, rTMS, epilepsy.

Terapia experimental da epilepsia com estimulação magnética transcraniana: ausência de melhora adicional com tratamento prolongado

RESUMO - *Objetivo*: investigar o efeito de três meses de estimulação magnética transcraniana repetitiva (EMTr) de baixa freqüência, na epilepsia de difícil controle. *Método*: Cinco pacientes (quatro homens, uma mulher, idades entre 6 e 50 anos), participaram do estudo; suas crises epilépticas não puderam ser controlados por tratamento medicamentoso e não tinham indicação cirúrgica; a EMTr foi realizada duas vezes por semana durante três meses, sendo que os pacientes anotaram o número diário de crises neste período, assim como nos três meses anteriores e posteriores ao tratamento. A aplicação da EMTr foi feita no vértex com bobina circular, com intensidade 5% abaixo do limiar motor. Durante as sessões de EMTr, 100 estímulos (5 séries de 20 estímulos, com um minuto de intervalo entre as séries) foram realizadas na freqüência de 0,3 Hz. *Resultados*: A média diária de crises (MDC) decresceu em três pacientes e aumentou em dois durante o uso da EMTr; um destes casos foi tratado somente por um mês; o melhor resultado foi encontrado em um paciente com displasia cortical focal (redução de 43,09% na MDC). Em todo o grupo de pacientes, houve decréscimo significativo na MDC de 22,8% ($p<0,01$). *Conclusão*: Embora o tratamento prolongado com a EMTr seja seguro e tenha sido registrado decréscimo moderado da MDC em um grupo de pacientes com epilepsia de difícil controle, respostas individuais de pacientes foram imprevisíveis e a relevância clínica deste método é provavelmente baixa. Nossos dados sugerem, contudo, que pacientes com lesões corticais focais podem ser beneficiar deste novo tipo de tratamento. Estudos futuros devem se concentrar neste grupo de pacientes.

PALAVRAS-CHAVE*:* estimulação magnética transcraniana, EMTr, epilepsia.

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Since its introduction in 1985[1], transcranial magnetic stimulation (TMS) has been used as a neurophysiological research tool[2-5] and more recently, following studies that showed a significant effect of repetitive transcranial magnetic stimulation (rTMS) upon cortical excitability[6-8] it has also been considered for the treatment of pathological conditions in which brain excitability is probably abnormal, such as in writer's cramp[9] and depression[10]. Modulation of cortical excitability by TMS in epilepsy was first attempted as a means of causing a silent epileptic focus to become active; this would be useful in the pre-operative evaluation of epilepsy surgery patients. However, despite encouraging initial results[11] it was subsequently found that single pulse TMS rarely, if ever, induces seizures, even in epileptic patients[12]. On the other hand, repetitive, rapid-rate TMS may precipitate seizures even in normal subjects, depending on stimulus rate and intensity[13]. Low-frequency rTMS appears to decrease cortical excitability for some time after stimulation sessions[14].

Recently, two studies have used low-frequency rTMS as a means of decreasing cortical excitability in epileptic patients[15,16]. Tergau et al.[15] studied nine epileptic patients, using rTMS at a frequency of 0.3 Hz, in daily sessions, for a period of five days, and found a 20 % decrease in the mean weekly number of seizures in one patient; other three patients had a decrease between 20 and 50%, and another three subjects had a decrease of over 50%. Comparisons were made between one month periods immediately before and after treatment. Menkes and Gruenthal[16] treated one patient with focal cortical dysplasia with bi-weekly low frequency (0.5 Hz) rTMS sessions for a period of one month. Daily seizure frequency was recorded for three months before rTMS sessions, during the month of treatment and for another month after the last experimental session. This patient had a decrease of 70 % in the number of seizures during the four weeks of rTMS treatment, compared to the other two months. Since epileptic patients may show spontaneous variability in seizure frequency which often persists for more than just a few weeks, these studies could have been biased by these random fluctuations. In a recent, randomized, blinded trial of rTMS in patients with localization-related epilepsy, patients were also treated for only one week[17]. This latter study had several important differences with respect to the previous ones: it used a higher rTMS frequency (1 Hz), a butterfly coil and suprathreshold stimuli.

Therefore, we decided to study a smaller group of patients, but to follow them for a much longer period of time, i.e., nine months (three months of treatment, and equal periods of observation before and after rTMS sessions). We also followed more closely the rTMS methods that had proven successful in the initial studies by Tergau et al.[15] and Menkes and Gruenthal[16].

METHOD

Five patients (four males, one female; ages 6 to 50 years) participated in the study. All had a diagnosis of medically intractable epilepsy and surgery was not indicated (one patient had already been operated on without satisfactory results). All had very good compliance with medical prescriptions. Table 1 summarises the clinical data of all patients and EEG data are shown in Table 2. Medications were not discontinued in any patient, and were kept unchanged throughout the whole study: four patients were on carbamazepine (SLBS, LAFC, MOP and OM); LAFC also used topiramate and OM, clobazam; RM was on lamotrigine, phenytoin and phenobarbital.

The experimental protocol was approved by the Health Sciences Faculty Ethics Commitee and all subjects (or their parents in the case of the child) gave written informed consent for the study. A Dantec Mag-Lite® Magnetic Stimulator (Skovlunde, Denmark) was used. Subjects sat comfortably on a chair. A round coil was positioned over the Cz position of the international 10-20 electrode placement system.

Prior to each session, motor threshold was determined; it was defined as the lowest intensity that produced a visible twitch of the relaxed abductor pollicis brevis (APB) muscle following at least 3 out of 5 test stimuli. When the coil was positioned with side A upwards (anti-clockwise current flow in the coil), the left motor cortex was predominantly stimulated and the twitch was more easily produced in the right APB; the opposite was true for side B of the coil. In order to ensure equal treatment of both hemispheres, stimulating sides were alternated between successive days of treatment (e.g., if on the first day stimulation was done with side A, on day 2 side B was used). A daily session consisted of 5 sets of 20 stimuli each, delivered at a frequency of 0.3 Hz at an intensity 5% below motor threshold (i.e., if motor threshold was 45% of maximal stimulator output, then stimulation was carried out at 40% of maximal stimulator output). Sets of 20 stimuli were separated from one another by one minute intervals. The first patient enrolled in the study, SLBS, was treated for one month. However, due to the spontaneous variability in seizure frequency over relatively

Table 1. Clinical characteristics of the patients enrolled in the study.

Patient	Age (Years)	Sex	Diagnostic hypothesis	Seizure characteristics
SLBS	32	M	Temporal focal epilepsy	CPS (secondarily generalized),TCGS
LAFC	19	M	Frontal focal epilepsy	CPS with complex automatisms
MOP	6	F	Frontal focal epilepsy	Asymetrical tonic seizures; CPS with complex automatisms
RM	30	M	Frontal focal epilepsy	Tonic seizures
OMA	50	M	Temporal focal epilepsy	CPS and TCGS

CPS, complex partial seizures; TCGS, tonic-clonic generalized seizures

Table 2. Electroencephalographic characteristics of the patients enrolled in the study.

Patient	Electroencephalographic findings
SLBS	Left temporal slow activity and sharp waves
LAFC	Left frontal slow activity and generalized sharp waves
MOP	Left fronto-central slow activity ; no sharp waves
RM	Bilateral frontal slow activity; no sharp waves
OMA	Bilateral temporal slow activity and sharp waves

long periods of time in this and other epileptic patients, we decided to increase treatment duration to 3 months in all subsequent patients. The number of daily seizures was recorded by the patients or their parents in a diary especially designed for these experiments. A comparison was made between seizure frequency in the treatment period and in the three months preceding and following rTMS treatment.

Repeated measures ANOVA was used for statistical analysis, with significance limits set at $p<0.01$. Post-hoc tests used included Scheffe F test, Dunnett t and Fisher PLSD. Since each patient served as his own control, mean daily number of seizures (MDNS) was compared in the three periods (before, during and after rTMS) both in individual patients (n= 270, i.e, the number of days in nine months) and in the patient group as a whole (n=1080, since the data for the patient who was treated for only four weeks could not be used for that analysis).

We did not use sham stimulation because the patients were critically affected by their epilepsy, with daily seizures, and there were two previous reports of significant benefits of rTMS in epilepsy[15,16]. We felt it would be unethical to deprive any patient from a treatment that had been described as effective in the literature.

RESULTS

Mean daily number of seizures (MDNS) decreased in three patients and increased in two during rTMS- one of these was treated for only one month; the best result was achieved in a patient with suspected focal cortical dysplasia (reduction of 43.09% in MDNS). In the whole patient group, there was a significant ($p<0.01$) decrease in MDNS of 22.8 %.

Table 3 shows the mean number of seizures in each patient before, during and after treatment, as well as the results of statistical analysis.

Although patient LAFC showed a steady decrease in MDNS during the whole experimental period, this trend was not statistically significant; MOP also had a decrease in MDNS that did not reach statistical significance; RM, on the other hand, showed a significant decrease in MDNS, followed by an equally significant increase upon discontinuation of the treatment. The remaining two patients, SLBS and OMA, did not improve and even increased their MDNS; this increase, however, was not statistically significant.

Taking together the data from all patients, MDNS was 1.426 (SE=0.089) before treatment, 1.100 (SE=0.073) during treatment and 1.613 (SE= 0.105) after treatment. MDNS during treatment was significantly lower than before or after treatment (ANOVA, $p<0.01$).

An interesting result was obtained when a

Table 3. Mean daily number of seizures (MDNS) for each patient before, during and after rTMS treatment.

Patient	pre TMS MDNS	MDNS during TMS	post TMS MDNS	Significant comparisons (ANOVA, p <0.01)
SLBS	0.154 (SE=0.072)	0.192 (SE=0.079)	0.192 (SE=0.136)	none
LAFC	0.506 (SE=0.124)	0.470 (SE=0.125)	0.361 (SE=0.087)	none
MOP	1.951 (SE=0.137)	1.765 (SE=0.125)	1.852 (SE=0.140)	none
RM	2.970 (SE=0.159)	1.690 (SE=0.152)	3.710 (SE=0.205)	pre X during pre X post during X post
OMA	0.247 (SE=0.082)	0.432 (SE=0.111)	0.481 (SE=0.129)	none

SE, standard errors.

comparison was made of the number of seizures on the day immediately following an rTMS session in the only patient who showed a significant decrease in MDNS (RM): the mean number of seizures on those particular days was significantly lower when rTMS had been carried out with side B of the coil facing upwards, thus stimulating preferentially the suspected pathological (right) cerebral hemisphere. This difference is shown in the Figure.

DISCUSSION

This study partially confirms previous observations that slow-rate rTMS is capable of decreasing seizure frequency in epileptic patients[15,17]. However, the reduction in seizure frequency was not as impressive as in those studies, which employed short courses of rTMS treatment; our results are more in keeping with those of a recent randomized, blinded trial, in which patients were also treated for just one week, with slight reductions in seizure frequency[16]. Those authors speculate that maybe more prolonged periods of rTMS treatment would result in more robust responses. However, their methodology was quite different from that employed in the other reported studies, including ours, and that may have been the reason for their lack of more impressive results. As to prolongation of treatment time, in spite of having treated four patients for three months, we have not found an enhancement of the previously described effects of rTMS.

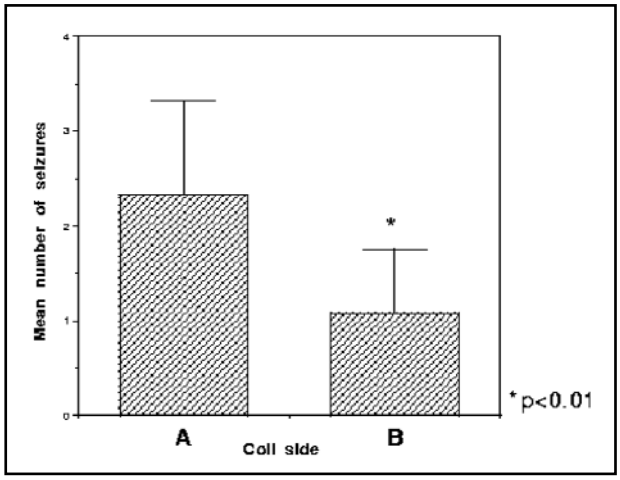

Figure. Mean number of seizures for patient RM on the days immediately after rTMS, with either side A of the coil facing upwards (A) or side B positioned in the same way (B). Error bars are standard deviations. The number of seizures was significantly lower when side B was used (Student t-test, p < 0.1). This coil position preferentially stimulated the suspected pathological (right) cerebral hemisphere.

There were no untoward effects from prolonged rTMS treatment. There was a significant variability in the responses of individual patients to rTMS: the patient who experienced the most significant decrease in MDNS was RM, who has a focal cortical dysplasia; this result is in accordance with the report by Menkes and Gruenthal[16], who were able to produce a dramatic decrease in seizure frequency in a patient with a similar lesion. Theodore et al.[17], although using different stimulation frequencies, suprathreshold stimuli and a butterfly coil, also point out a tendency for patients with neocortical rather than mesial foci to have a greater mean reduction in seizure frequency. Consistent with that view, we have been able to demonstrate a significant decrease in the number of seizures experienced by patient RM on the days immediately following preferential stimula-

tion of the suspected pathological cerebral hemisphere (Figure).

On the other hand, the two patients who showed a complete lack of improvement (SLBS and OMA) either had extensive brain lesions (OMA) or a lesion in a location which is certainly completely out of reach for rTMS (mesial temporal sclerosis in patient SLBS).

Future research into this new treatment modality should probably concentrate on those patients with neocortical abnormalities and try to apply focal rTMS to the pathological area, since our study and those of Menkes and Gruenthal[16] and even Theodore et al.[17], all suggest that a clinically significant effect would be more likely under such circumstances. As far as other epileptic disorders are concerned, however, our data suggest an effect that, although interesting and statistically significant if this small and heterogeneous group of subjects is considered as a whole, is not significant for individual patients and is of doubtful clinical relevance. The one exception, again, is the patient with a diagnostic hypothesis of a neocortical lesion.

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