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Original Article

Effect of low-frequency repetitive transcranial magnetic stimulation on sleep pattern and quality of life in patients with focal epilepsy

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ABSTRACT

Objective: In this study we analyzed the effects of transcranial magnetic stimulation (TMS) on sleep and on the self-perceived quality of life in epileptic patients.
Methods: A total of 24 male patients diagnosed with focal epilepsy were included in the study. Pharmacological treatment with levetiracetam was standardized at 2 g daily. Before TMS onset, all-night polysomnographic recording (PSG) was performed, and the Quality of Life in Epilepsy Inventory (QOLIE-31) was administered. Thereafter, patients underwent low-frequency repetitive TMS (1000 pulses/1 Hz) daily for 10 days. After the end of the treatment, a second polysomnographic study was performed, and the QOLIE-31 questionnaire was administered again.
Results: TMS induced a significant increase in sleep efficiency and in total sleep time, along with a decrease in sleep latency and the number of awakenings. In addition, the number of interictal discharges during sleep decreased significantly. Concerning the QOLIE-31 scale values, the patients showed great improvement in the self-perceived quality of life.
Conclusion: The present results indicate that TMS may mediate therapeutic effects in the treatment of patients with focal epilepsy, and that TMS treatment is accompanied by improvement of sleep patterns as well as improvement in self-perceived quality of life. However, a study that includes a control group undergoing sham stimulation is needed to confirm these findings.

1. Introduction

Epilepsy is a neurological condition in which convulsive and/or nonconvulsive seizures occur on a recurring basis. Its prevalence in industrialized countries ranges from 3 to 4 per 1000 persons, but reaches up to 57 per 1000 persons in developing countries [1]. This disorder affects 50 million persons worldwide, and approximately 30% of these patients do not respond to conventional treatments [2]. The pathophysiology of epilepsy includes a state of abnormal cortical excitability caused by the generation of paroxysms due to changes in the polarity of the cell membrane, increasing hypersynchronization of neuronal networks. This state causes abnormal hyperexcitable neurons to fire, causing partial or general propagation, producing clinical manifestations [3,4]. The classification of epilepsy, in its latest review by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE), refers to forms of epilepsy as focal or generalized [5]. Conventional treatment is based mainly on the use of drugs aimed at reducing this pathological hyperexcitability, either by reducing or by blocking neuronal excitability.

On the other hand, transcranial magnetic stimulation (TMS) is a noninvasive technique that has recently been reported as an effective therapy for some neurological diseases [6]. Repetitive TMS can be divided into two types: fast-frequency stimulation (>5 Hz), and slow-frequency stimulation (≤1 Hz) [7]. Slow-frequency stimulation has been used in several neuropsychiatric disorders in which neuronal hyperexcitability might be involved. Positive results have been reported for depression [8], posttraumatic stress disorder, obsessive compulsive disorder, mania, schizophrenia [9], Tourette syndrome, Parkinson's disease, dystonia, multiple sclerosis, and myoclonus [10], among others. Furthermore, when TMS was used in posttraumatic stress disorder and major depression, besides the improvement in symptoms, changes in sleep patterns were reported [11].

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In a recent study in our laboratory, we treated patients with insomnia associated with abnormal electroencephalogram (EEG) activity (sharp waves and phase inversion spikes), and found that after 10 days of continuous treatment with low-frequency TMS, abnormal EEG activity decreased and sleep improved significantly [12]. Patients with epilepsy often complain of disturbances of sleep initiation and continuity. They also report insomnia associated with restless sleep, even when they have controlled daytime seizures, which could be directly affecting their quality of life [13].

The goal of the present study was to assess the influence of low-frequency TMS on sleep pattern and quality of life in epileptic patients already being treated with levetiracetam. We hypothesized that low-frequency TMS would decrease EEG epileptogenic activity, inducing an improvement of the sleep pattern as well as an improvement in self perceived-quality of life.

2. Methods

2.1. Study subjects

A total of 24 male patients (mean age 34 ± 10.5 years) with metabolic/structural focal epilepsy [5] and under treatment with levetiracetam (2 g/day) were included in the study. The test was carried out taking into account the statements on Biomedical Research in Humans described in the General Health Law, Sections 96 to 103, 2007. All participants voluntarily agreed to participate and signed an informed consent form. The patients were under medical surveillance beginning with the standardization of pharmacological treatment, during the PSG tests and TMS application until the end of the protocol. Sleep studies were performed at the Sleep Disorders Center UAMI. Patients were recruited at the ABC Medical Center of Santa Fé, Mexico City, where standardization of the pharmacological treatment and TMS and the administration of the QOLIE-31 questionnaire were performed.

2.2. Experimental design

Antiepileptic treatment was standardized for all of the patients at least three months before the onset of the study (levetiracetam 1 g every 12 hours). QOLIE-31 was administered to all participants. As well, a baseline PSG study was performed in all participants. Patients were excluded if they presented with the following: a psychiatric disorder; a neurological disorder other than epilepsy or a sleep disorder; drug abuse; or uncontrolled seizures (ie, when pharmacological treatment was unable to decrease seizure frequency to less than 50%).

Once the baseline data were recorded, TMS therapy was initiated. The TMS paradigm consisted of a 1-Hz stimulation applied in trains of 10 seconds followed by an interval of 5 seconds without stimulation. This sequence was repeated 100 times, lasting 25 minutes in total for the application of 1000 pulses. This stimulation in each patient was applied daily at 7 a.m. for 10 days. Stimuli were delivered using a Magstim Super rapid stimulator (Magstim, London, UK), connected to a figure-of-eight coil. During stimulation, patients remained comfortably seated in a chair. TMS was applied over the region with epileptic activity, based on recently described medical guidelines [14]. Thus, TMS was applied to the left hemisphere in the frontal region (n = 10), the temporal region (n = 12), and the parietal region (n = 2). Between 24 and 72 hours after completion of the therapy, a second application of QOLIE31 was administered, and a second PSG record was performed. The time elapsed between the first and the second PSG was between two and four weeks.

2.3. Techniques

The QOLIE-31 questionnaire was administered to assess self-perceived quality of life in patients with epilepsy. This questionnaire consists of 31 items divided in seven domains: seizure worry, overall rating of quality of life, emotional well-being, sensation of energy or fatigue, cognitive functions, effects of medication, and social relations. It is a self-administered questionnaire. The results are converted to a scale from 0 to 100 to determine the quality of life; the lower the score is, the lower the quality of life [15]. Values below 40 reflect self-perceived poor quality of life. Values between 41 and 60 reflect self-perceived good quality of life. Values above 61 reflect self-perceived excellent quality of life [16].

The all-night sleep recording was performed using a 10-20 international standard setup of electrodes, to allow detection of epileptiform discharges, in addition to EEG activity. Also, an electrooculogram (EOG), electromyogram (EMG), electrocardiogram (EKG), nasobuccal airflow, thoraco-abdominal movement, oxygen saturation, and body position, were recorded. The number of epileptiform discharges was counted throughout the entire record. PSG studies were done using a Cadwell easy 2, version 2 (Cadwell Industries Inc., USA).

2.4. Statistical analysis

Data were analyzed using the SPSS version 17 software (SPSS Inc., Chicago, IL, USA). A Student *t*-test was used for related samples to compare the results concerning the number of epileptiform discharges, the parameters of sleep components, and the values of the QOLIE-31 questionnaire, before and after treatment. When proportions were analyzed, a χ^2 test was used.

3. Results

During the TMS procedure, there were no epileptic seizures. Fig. 1 shows the number of epileptiform discharges recorded before and after TMS treatment. Although the number of events decreased significantly after TMS stimulation, all of the patients still showed these paroxysms. Patients reported a mean seizure frequency of 13.7 in the month before TMS that decreased to a mean of 6.5 in the month after TMS.

Concerning the sleep pattern, Table 1 summarizes the results obtained. As can be seen, total sleep time increased significantly. After TMS, total sleep time increased from a mean of 6.1 hours to a mean of 7.1 hours, reaching normal values reported for healthy persons

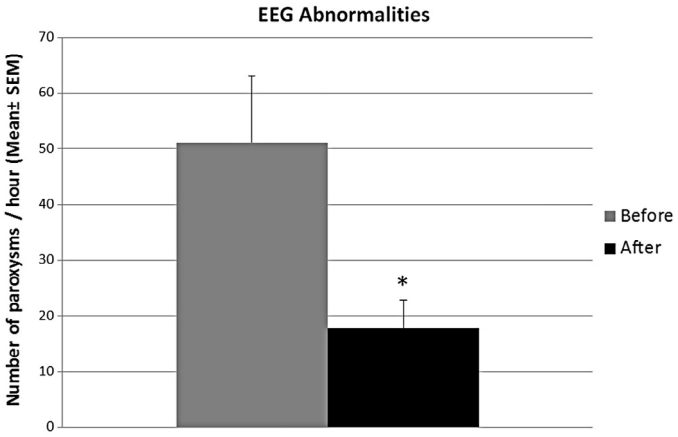

Fig. 1. Number of epileptiform discharges during sleep time in epileptic patients treated with levetiracetam, before and after low-frequency transcranial magnetic stimulation. *$p < 0001$, *t*-test.