

Modification in Pittsburgh Sleep Quality Index after low intensity transcranial magnetic stimulation in patients with fibromyalgia

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Abstract

Objective

Fibromyalgia is a disease of unknown origin in which sleep involvement is very prevalent, and one of the main symptoms, even as prevalent as pain. In fact, one condition has been linked to the other, and the two may feedback on each other. We investigated what happens if by applying low-field magnetic stimulation in patients with fibromyalgia, it could improve sleep variables, and if this would be related to an improvement in the pain of the patients.

Methods

We compared the results of a group of female patients with fibromyalgia, who underwent treatment for 6 weeks, with another group of patients with similar characteristics, who were not treated. The results were also compared with a group of healthy women, who served as a second control group. The Pittsburgh sleep scale was used as a sleep scale and a global clinical scale was used to assess general state.

Results

A significant improvement was observed in the different items of the sleep scale applied, from the four weeks of treatment, being even more evident at the end of treatment at six weeks. A total of 82% of patients improved at the end of treatment. There was a correlation of this improvement with the overall pain situation of the patients. In addition, there was a trend towards equal sleep outcomes between treated patients and healthy subjects.

Conclusion

Treatment with low intensity magnetic stimulation could improve the sleep of fibromyalgia patients, as well as their overall clinical situation, and both processes could be interrelated.

Key words

central sensitisation syndrome, chronic pain, LITMS, PSQI, sleep disorders

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Introduction

Fibromyalgia (FM) is a challenging disease for the patients who suffer from it and for the clinicians who treat it (1). Its main feature is the chronic widespread pain felt by patients. It is a very common syndrome, estimated to affect up to 5% of the population (2), with the majority being women (90%) (3). Most scientists now believe that the condition originates in the central nervous system, caused by an alteration in signal processing (4-5).

Although pain is the predominant symptom, other symptoms that are very prevalent in this pathology are fatigue, mood problems, neurocognitive difficulties and sleep disorders (6). In fact, for many authors, sleep problems are, after generalised pain, the most common symptom, being reported in more than 90% of patients (7-10). This difficulty in achieving unrefreshing sleep has negative effects on patients' quality of life, being related to the other symptoms described above, such as fatigue, neurocognitive problems and patients' mood problems (11-16). Some authors explain FM as a primary sleep problem (17), while for most researchers the relationship is bidirectional (7, 18), entering a vicious circle, in which continuous pain causes sleep problems, and sleep disturbances increase pain (19-21).

FM currently has no curative treatment. Therefore, all currently available treatments are aimed at relieving symptoms. They are mainly based on drugs with neuromodulatory action, such as antidepressants or antiepileptic drugs, with low efficacy, and with side effects to be taken into account (22-23). Among the new therapies for the treatment of this disease is transcranial magnetic stimulation (TMS), one type of which is low-intensity transcranial magnetic stimulation (LITMS) (24). This technique is believed to act by modulating brain oscillatory activity, and is being used to improve patients' symptomatology, such as pain or sleep, even its effects are sustained in the long term (24, 25). Our working hypothesis is that LITMS improves the sleep pattern of patients, and this would correlate with an overall improvement.

Materials and methods

Participants

Patients and controls were recruited between January and December 2019, belonging to the same geographical area (Madrid, Spain). All of them gave their signed consent to participate in the study, subject to approval by the Centre's Ethics Committee (no. 2018/14/190), and the study was conducted in accordance with the standards required by the Helsinki Declaration. A total of 79 patients, all women with fibromyalgia, participated in the study, and a total of 52 healthy women as a control group.

All patients had to have been diagnosed with fibromyalgia prior to their participation in the study, with at least 2 years of evolution, with a moderate to high degree of severity according to the global clinical rating scale, and the diagnosis had to have been ratified by at least two specialists in this pathology, following the standard classification and diagnosis guidelines (following the ACR 1990 classification criteria and the new 2010 diagnostic proposal of this Academy) (26-27). In order to homogenise the sample as much as possible, only women aged between 18 and 65 years were selected, since, as explained before, this is the group of subjects most commonly affected. Participants were not required to have other diseases that could interfere with the final results, such as severe psychiatric problems (*e.g.* major depression), major sleep disorders (*e.g.* narcolepsy), or diseases that are associated with poorer sleep quality, as in many other neurological diseases (*e.g.* Alzheimer's disease) or respiratory diseases (*e.g.* COPD).

All patients were administered the scales used in the study, which were the patient clinical global impression scale and the Pittsburgh questionnaire, both at the beginning and at the end of the study. An independent investigator randomly selected which group of patients received treatment with LITMS. Therefore, 3 distinct groups were established; G1: women with fibromyalgia treated with LITMS, G2: women with fibromyalgia not treated with LITMS, and G3: control group of healthy women.

Competing interests: none declared.

The untreated group (G2) was selected as similar as possible to the G1 group in terms of biodemographic, clinical and therapeutic characteristics. The control group (healthy subjects) was also selected taking into account their biodemographic characteristics similar to those of G1 and G2, and that they did not have any other disease or treatment that could interfere with the study, as indicated above.

Treatment

This is a prospective, interventional, experimental study with two arms and a control group. Patients who opted for treatment (G1) underwent 6 sessions, one per week, of LITMS. After 4 sessions, patients were given the clinical questionnaires again for an interim control. This intermediate control was chosen because significant differences were found in previous studies from this point onwards (24, 25). The last and definitive control was carried out at 6 weeks.

LITMS is a form of TMS that consists of the application of a brain device (Fig. 1), which seeks neuronal stimulation with very low frequencies (around 30 picoTeslas), typical of physiological brain activity, and close to 8 Hz of frequency (within alpha brainwave range). This treatment has been assigned patent WO 2011/098638 and is approved by the Spanish Agency for Medicines and Health Products and has quality assurance certificate CE0318. Each application lasts 20 minutes, and must be carried out in a suitable enclosure, using a Faraday cage, where the electromagnetic field is practically null. The patient is lying down during the treatment, inside the Faraday cage, wearing a cap with the coils placed inside the cap. The patient must be at rest and calm during the session. The mode of action of LITMS is believed to act through the so-called “window effect”, activating neural networks by resonance. These networks are selective, only those whose resonance coincides with the applied frequency will respond, not affecting the rest. It is a very safe and painless treatment, which has already been shown to be effective in this type of patient, and has been ap-



Fig. 1. Magnetic stimulation generator and brain device with embedded coils applied in the study.

proved for use in fibromyalgia patients in our country (24), and its effect has been shown to be maintained in the long term (25).

Data collection

Sociodemographic characteristics of patients and controls were collected by means of a self-administered questionnaire, including gender, age, years of evolution, mean analgesic or neuro-modulatory treatments, and patients/controls not taking any medication.

To assess sleep quality, we use the Pittsburgh Sleep Quality Index (PSQI) (28), which was developed by Buysse *et al.* in 1989, and has since been routinely used in multiple studies assessing sleep quality in countless pathologies. The results of this questionnaire are grouped into seven sleep-related areas: latency, duration, subjective quality, efficiency, associated sleep disorders, use of sleep medication and daytime dysfunction. The scores are evaluated on a scale from 0 to 3, with 3 being the most negative value. The subdomain values are summed to give a total ranging from 0 to 21, with higher values indicating poorer sleep quality. The scale is classified into good sleep quality (0–5 points) and poor sleep quality (>5 points). The PSQI has demonstrated adequate internal consistency, sensitivity and specificity for sleep assessment (29). A global clinical patient rating scale (CGIp) was used to

assess the general health status of the patients, with a range between 0 and 3, where 0 means good general health status, with 3 again being the worst value.

Statistical procedure

First, a descriptive (mean, standard deviation, frequencies and percentages) and inferential analysis was performed. The normality of the data distribution was checked using a Kolmogorov-Smirnov test. A multivariate analysis of variance (MANOVA) was performed to examine the relationship between different aspects of sleep with the PSQI scale and global improvement with the CGIp scale, in FM. F-statistic analysis was performed using Wilks' lambda. Statistical significance was $p < 0.05$. All analyses were performed with SPSS software (v. 20.0).

Results

The baseline data of patients are shown in Table I. The entire sample of patients completed the treatment and no side effects were recorded in any case. To compare the data between the different scales, two Manova tests were performed. The first compared the PSQI with the CGIp variance, with results respectively of $p_1 = 0.0099$ and $p_2 = 0.038$, indicating statistical significance in both cases. The Wilks' lambda resulting from this comparison was 0.754, again indicating that the results are statistically significant for 75.4% of

Table I. Baseline data of patients (G1 and G2) and controls (G3).

Group	G1	G2	G3
Number	27	52	52
Age (range)	30-63	24-65	30-64
Age (average)	46+9	48+9	45+10
Evolution (years)	8,5	8	NA
Diagnostic (years)	3,5	5	NA
Without medication	8	11	NA
Drugs	2,5+2	2,1+2	NA

NA: not applicable; drugs: average and standard deviation of different drugs taken by patient.

Table II. Score at Pittsburgh and clinical global impression across sessions.

Score Pittsburgh	Session 1	Session 4	Session 6
Media	15.67	10.41	8.29
Standard deviation	3.88	4.00	3.67
CGIp			
Media	2.93	1.89	1.63
Standard deviation	0.27	0.75	0.56

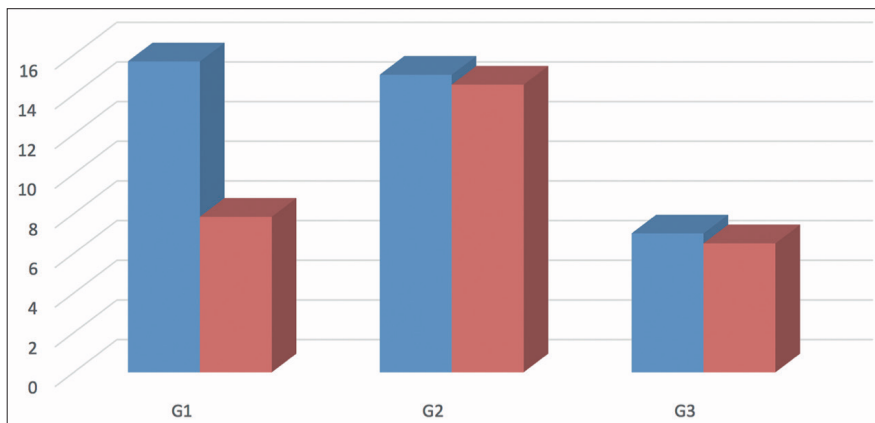


Fig. 2. Bar chart with the total score on the Pittsburgh Scale, before and after the treatment. G1: patients treated with LITMS. G2: patients not treated with LITMS. G3: control group.

the sample. Another Manova was also developed comparing the total variance in the PSQI with the variance in the CGIp. In this case, $p1=0.0083$ and $p2=0.042$ were obtained, both below the established significance of 0.05, again indicating significant results. For this comparison, Wilks' lambda rises to 0.984, which implies that it is valid for 98.43% of the sample.

In the case of the PSQI total score, as can be seen in Table II and Figure 2, a significant reduction was achieved in the group of treated patients, from 15.67 to 7.84 ($p<0.005$), approaching the values of the control subjects). In the case of the control group (G3), being a group of healthy women, their Pittsburgh score was 5.37 on average

with a standard deviation of 3.21, significantly lower than in women with fibromyalgia.

When we analysed the group of patients treated (G1), we observed an improvement in all subdomains of the PSQI, all of them with statistical significance ($p<0.05$), except in item 6 (use of medication), being more striking at the end of the 6 sessions (Table III).

The secondary objective of this study was also to find out in how many patients the treatment did not work, either because of a worsening in any of the indices studied, or because they did not experience an improvement in any of them (Pittsburgh or CGIp). For this purpose, different variations are studied:

- The first variation (V1) comprises a study prior to the start of treatment and data collection on the day of the fourth session, at which time continuity is determined according to the results obtained. In this variation, there were 14.81% of women who experienced no improvement and no subject worsened their score on the Pittsburgh scale. As for the CGIp there were 22.22% of people who did not experience any improvement, although again none worsened in the parameters studied.
- The second variation is from the test of the fourth session to the last one carried out on the day of the sixth and last session, so the period studied is two weeks. The Pittsburgh index remained the same in 44.44% of the cases and there were two subjects whose score worsened, corresponding to 7.4% of the sample. As for the CGIp study, 70.37% remained the same and only one subject worsened (3.7%).
- The last variation studied corresponds to the total treatment (from before the first session to the last). 100% of the subjects experienced some improvement with respect to the overall Pittsburgh index and one subject maintained his CGIp, as the rest of the participants improved. These variations are observable in the mean and standard deviation of the Pittsburgh index and CGIp over the sessions, with a greater effect in the last session compared to the intermediate session 4, for the group of treated women (recall that the Pittsburgh index is scored as 21 for poor sleep and 0 for optimal sleep, and that the CGIp is scored out of 3, with 3 being poor and 0 optimal quality of life) (Table II).

Finally, when comparing the results of only the group of treated patients (G1), between the perceived global quality, through the CGIp, and the global quality of sleep, through the PSQI we found a direct positive correlation. As can be seen in Figure 3, at the end of treatment, there were very few patients with high scores on both the CGIp and the PSQI, in contrast to what was observed at the start of treatment.

Table III. Scores by areas (items) and total Pittsburgh scale in treated patients (G1) throughout the study and statistical difference.

GROUP/ITEM	1° Session	4° Session	6 Session	Stat. Diff
ITEM 1	2.59	1.41	1.29	<0.01
ITEM 2	1.81	1.44	1.24	<0.05
ITEM 3	1.89	0.93	0.76	<0.01
ITEM 4	2	1.22	0.71	<0.01
ITEM 5	2.48	1.70	1.41	<0.05
ITEM6	2.11	1.78	1.70	0.10
ITEM 7	2.78	1.93	1.65	<0.05
TOTAL	15.67	10.41	7.84	<0.05

Items. I1: sleep latency. I2: sleep duration. I3: sleep quality. I4: sleep efficiency. I5: associated sleep disorders. I6: medication. I7: daytime dysfunction.

Discussion

The aim of this study was to determine whether there is a correlation between overall patient improvement and sleep quality in a group of women with FM, using a non-invasive brain stimulation treatment such as LITMS, and comparing the effect with a control group of healthy women.

The results of the study show that after applying 6 weekly treatment sessions, patients perceive a clear improvement in general, as well as in the different evaluation parameters of the Pittsburgh scale, except in the use of medication. Moreover, there is a positive correlation between these parameters, being more significant when more sessions were applied.

The various symptoms that occur in a patient with FM, in addition to pain, together with the rest of the symptoms, currently imply that there is a dys-

function of the central nervous system (CNS) (29). After widespread pain, the most common complaints in FM, next to fatigue, are sleep disturbances, described by more than 90% of patients in different studies (7-10).

Multiple experimental studies have demonstrated a bidirectional relationship between sleep and pain. Continued pain reduces sleep quality, and sustained sleep deprivation increases pain (18-19). The causal relationship between the two is not entirely clear, while some authors suggest that two-thirds of FM cases are due to sleep disturbances (17), and these correlate with the severity of pain and even the number of tender points (30), others, however, do not consider sleep as a pathogen of FM (31-32).

Indeed, more than 45 years ago, Moldofsky experimentally described that disruption of deep sleep induced widespread pain and fatigue in healthy

subjects (33), and concluded that changes in sleep/wakefulness can produce hyperalgesia or bodily hypersensitivity and fatigue. Since then, multiple studies have described the interaction between sleep and pain, some based on global sleep deprivation, others on specific deep sleep or REM sleep deprivation, even in healthy subjects (29). There is evidence that sleep fragmentation in healthy subjects interferes with the inhibitory response of the nervous system to painful stimuli, and increases sensitivity to different non-painful stimuli, such as noises, bright lights or intense odours (33-34), reflecting a sensitisation of the CNS (36), a concept common to the so-called central sensitisation syndromes (29).

We know that sleep disruption in normal subjects can reduce inhibitory descending pathways (34, 38), and even that sleep deprivation in a population of sedentary middle-aged women causes an alteration of these descending pathways similar to that observed in FM patients (34). As these modulatory circuits are also important in the pathophysiology of anxiety and depression, one study wanted to compare in fibromyalgia patients and healthy subjects who had undergone experimental pain, what their levels of anxiety, depression, sleep and other FM symptoms were like. Sleep quality (measured with the PSQI) was the only factor that correlated significantly with the reduction

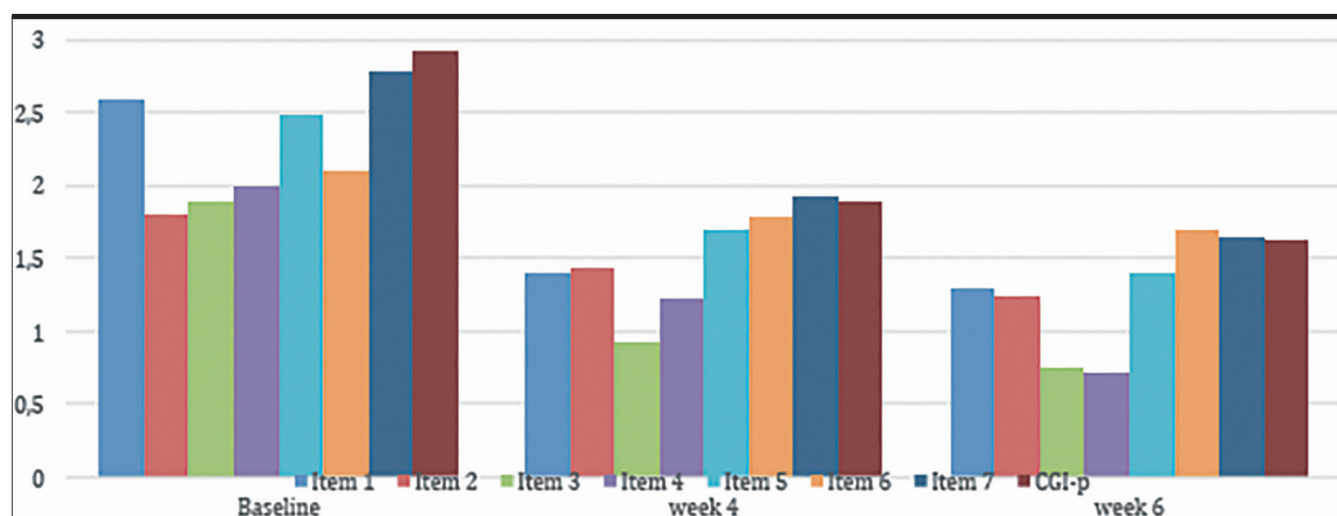


Fig. 3. Bar chart comparing the variations across the weeks with the Pittsburgh Scale (with the 7 items analysed) and the CGI-p in treated patients (G1). CGI-p score (between 0 and 3) and the Pittsburgh Scale (a value of 0 is assigned if the score is between 0 and 5, both included. Value 1; between 6 and 10 both included. Value 2; between 11 and 16 inclusive and value 3; between 17 and 21 inclusive).

of descending inhibitory pathways in fibromyalgia patients ($p=0.006$) (39). Furthermore, this vicious circle leads to the onset or aggravation of other symptoms, such as cognitive and mood problems (11-12, 20-21). Sleep deprivation affects the patient's mental alertness, memory, concentration and general mood (39). Patients with poor sleep quality are more likely to have pain and fatigue, defining symptoms of FM (10), as well as increased anxiety and depression (41-42). Poor sleep quality has been reported to have a cumulative effect on the development of depression (43). So much so that, along with cognitive symptoms, fatigue and waking with a sense of unrefreshing sleep are the cardinal symptoms of severity for the new American Academy of Rheumatology diagnostic criteria for FM (27). This reflects a broader change in criteria than the old criteria for classification of FM by this Association, dating back to 1991, when only the symptom of pain was included (26). A large number of studies have correlated different polysomnographic changes and FM. Altered sleep architecture has been described with delayed sleep onset (44-45), poor sleep efficiency (46), reduced deep and REM sleep (44-45, 47) and various non-REM sleep disturbances, including alpha rhythm prominence, commonly referred to as alpha rhythm intrusion or alpha-delta sleep (44, 46-49). This disturbance has been associated with an increased number of pain points, increased pain duration and intensity, and decreased sleep duration and efficiency (48). The significance of all these alterations in FM has not been fully elucidated; in fact, other chronic diseases have been commonly associated with these sleep variations (47). Even in patients with insomnia without other associated pathology, none is considered specific to FM (40, 50). The Pittsburgh scale is the most widely used self-administered questionnaire in research on the relationship between FM and sleep (33). Researchers who have analysed sleep in FM with the PSQI have obtained assessments of poor subjective sleep quality in most cases and a significant prevalence of sleep problems in this population (8,

10, 51). Osorio *et al.* evaluated the sleep of 30 patients with FM and 30 healthy controls with this instrument, and highlighted that the group with FM, in addition to presenting poor sleep quality, had particularly affected PSQI dimensions related to sleep latency, the existence of sleep disturbances and impaired daytime functioning (52), findings similar to those found in our patients. It has been suggested that early recognition and subsequent treatment of sleep disorders would help to reduce the symptoms of this disease (53), as has been demonstrated in several clinical trials that have successfully reduced insomnia (54-55). In our case, after the application of an experimental treatment, such as LITMS, an improvement in sleep-related items was observed, and this correlated with the patient's overall improvement. We cannot know which of the two processes originally leads to the improvement of the other, as both are intrinsically related. Due to the limited patient sample we cannot draw definitive conclusions about efficacy, nor about the duration of the observed effect, but it opens up an interesting avenue for future study. As conclusions, sleep disturbances are not only one of the most common symptoms in fibromyalgia. The relationship between sleep disturbances and fibromyalgia is possibly bidirectional. Patients with fibromyalgia have systematically worse scores on the PSQI than controls, and the improvement in the different sleep parameters assessed by this questionnaire could be of great importance in the overall improvement of the disease. With our study, we have shown that after the application of a non-invasive treatment, such as the LITMS, an improvement is obtained in different areas related to sleep, such as subjective quality, sleep duration, sleep efficiency and dysfunction during the day. A second conclusion is that by applying a greater number of sessions, better results are obtained, although they are significant from the fourth session onwards. Finally, the improvement in the different sleep parameters correlates with the overall improvement of the patient, both cardinal aspects of fibromyalgia.

One of the limitations of this study is that it would be desirable to extend it to a larger number of participants, and to describe in future studies how long these clinical changes are maintained. It would also be very interesting to complete the results with a paraclinical test, such as a polysomnography, in addition to the clinical scales used. Even so, we believe that it opens up an interesting field of study and progress in the coming years in the knowledge of this pathology.

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