Comparison of alpha–theta neurofeedback versus sensorimotor rhythm neurofeedback in the treatment of patients with fibromyalgia: A randomized, double-blind, controlled clinical trial

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Original Article

Abstract

BACKGROUND: Fibromyalgia (FM) is a chronic disease with widespread musculoskeletal pain. In this study, we used neurofeedback to reduce pain and enhance the quality of life (QOL).

METHODS: We conducted a double-blind randomized controlled trial (RCT) in 40 patients referred to Tuba Specialized Clinic and Clinic of Imam Khomeini Hospital in Sari, Iran, between December 2013 and July 2015. Group 1 underwent sensorimotor rhythm (SMR) neurofeedback training and group 2 underwent neurofeedback training for alpha-theta training. The primary outcomes were pain reduction and increasing QOL, which were measured using Visual Analog Scale (VAS), Numeric Pain Scale, Fibromyalgia Impact Questionnaire (FIQ), and Medical Outcomes Study (MOS) Sleep Scale, respectively, within the first day, 4 weeks, and 8 weeks post-randomization.

RESULTS: A total of 46 patients were screened for eligibility and 40 patients completed the trial. In both groups, the differences between FIQ scores before and after the study were statistically significant ($P < 0.05$).

CONCLUSION: Neurofeedback training could be applied to reduce pain and improve the QOL of patients with FM.

KEYWORDS: Neurofeedback; Fibromyalgia; Pain

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Introduction

Fibromyalgia (FM) is one of the most common musculoskeletal syndromes in adults. It also encompasses symptoms such as fatigue and sleep disturbances, morning stiffness, paresthesia, headache, and mood and cognitive disorders.[1] The exact cause of the disease is unknown; however, some evidence indicates that FM is a non-inflammatory syndrome.[1,2] Onset of symptoms may be followed by a viral infection, psychological or physical damages, or may be slow and gradual with no clear cause.[1,2] Several factors have been reported to be responsible for the pathogenesis of this syndrome including autonomic nervous system (ANS) disorders, peripheral decrease in cortisol response to stress, increased levels of neurotransmitters in cerebrospinal fluid (CSF), low levels of growth hormone (GH), low levels of metabolites of serotonin in CSF, and sleep disturbances.[2] FM, after osteoarthritis (OA), is the most common diagnosis in rheumatology clinics.[3] The prevalence of this syndrome is 2 to

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7 percent and in various studies, the prevalence rate among women and men has been reported 0.7% to 13.0% and 0.2% to 3.9%, respectively.[2] FM is a multifaceted and complicated syndrome with relatively unpredictable process. Since the tolerance and response to treatment methods differs among patients, hence, choosing the most appropriate treatment for both the physician and the patient is difficult.[3] The main goals of treatment are reducing pain and improving sleep in patients.[1] Neurofeedback is one of the new methods introduced in the treatment of these patients, which is in fact operant conditioning of electrical activity of the brain.[4,5]

Over the past decade, neurofeedback has been used to treat a wide range of psychiatric disorders. One of the neurofeedback protocols is "sensorimotor rhythm (SMR) reinforcement" that its effectiveness in reducing the symptoms of FM has been reported.[6-8] Another protocols is "alpha-theta reinforcement" that is used to increase optimal and innovative performance, reinforce working memory, improve sleep quality, and treat anxiety disorders including generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), anxiety and depression associated with alcohol use disorders, and insomnia.[9-12] However, based on the available resources, this protocol has not been used in the treatment of FM so far.

New criteria mainly emphasize on the clinical symptoms of widespread pain (diffuse) and neuropsychological symptoms.[13] Patients, in addition to widespread pain, also complain about fatigue, stiffness, sleep disturbance [difficulty falling asleep, difficulty maintaining sleep, restless legs syndrome (RLS), and impaired breathing during sleep]. Analysis of genetic predisposing factors indicates the presence of neuropsychological routes shared with mood disorders and the role of the central mediators.[14] Feeling of pain in patients with FM is affected by emotional and cognitive aspects that provide a solid foundation for the use of cognitive, therapeutic, and behavioral strategies.[15,16]

Materials and Methods

In two referral centers, Tuba Specialized Clinic and Imam Khomeini Hospital in Sari, Iran, we randomized patients in a double-blind, randomized controlled trial (RCT) comparing the clinical consequences of alpha–theta reinforcement neurofeedback therapy versus SMR reinforcement neurofeedback therapy between December 2013 and July 2015. All of the patients were under treatment with 50 to 150 mg of pregabalin per day. Participants gave written informed consent at screening and were not paid for participating.

The study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari (Reference Number: IR.MAZUMS.REC.94-907). This trial was registered at the Iranian Registry of Clinical Trials (IRCT) (code: IRCT2015022111885N4).

We assessed the eligibility of all women with FM who referred to each of the two referral centers and were 18-50 years old. FM was diagnosed by a rheumatologist and based on American College of Rheumatology preliminary diagnostic criteria.[1] The exclusion criteria were being younger than 18 years and older than 50 years, the presence of infectious diseases, chronic diseases such as cancer, diabetes, history of cardiovascular disease (CVD), rheumatologic diseases [such as lupus, rheumatoid arthritis (RA), etc.], history of neck and spine surgery, psychological disorders [including psychotic disorders, major depressive disorder (MDD), bipolar disorder, substance abuse disorders], use of psychiatric drugs (antidepressants, anti-anxiety, hypnotic, etc.), the incidence of unbearable side effects caused by intervention during the study, or unwillingness to participate in the study.

A total of 46 patients were screened for eligibility and were randomized between December 2013 and July 2015 (Figure 1).
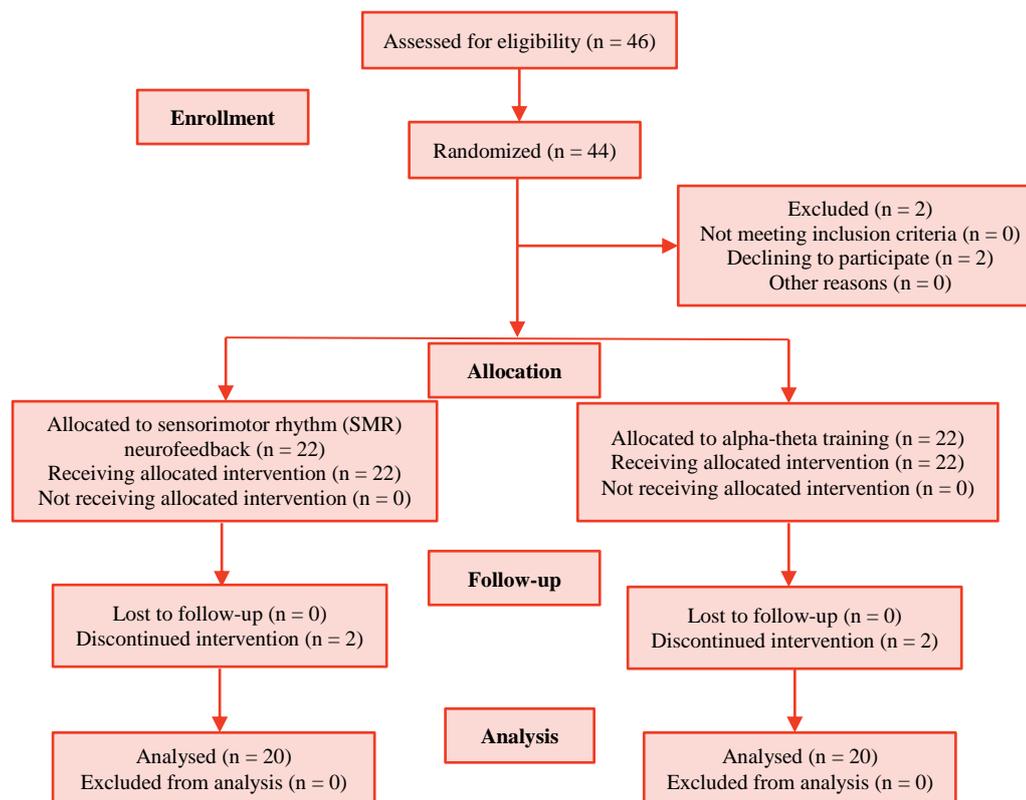
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                        ┌─────────────────────────────┐
                        │ Assessed for eligibility (n = 46) │
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   │ **Enrollment** │            ┌──────────────────────┐
   └──────────────┘            │ Randomized (n = 44) │
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	Excluded (n = 2)
	Not meeting inclusion criteria (n = 0)
	Declining to participate (n = 2)
	Other reasons (n = 0)

Allocation

Allocated to sensorimotor rhythm (SMR) neurofeedback (n = 22) Receiving allocated intervention (n = 22) Not receiving allocated intervention (n = 0)	Allocated to alpha-theta training (n = 22) Receiving allocated intervention (n = 22) Not receiving allocated intervention (n = 0)

Follow-up

Lost to follow-up (n = 0) Discontinued intervention (n = 2)	Lost to follow-up (n = 0) Discontinued intervention (n = 2)

Analysis

Analysed (n = 20) Excluded from analysis (n = 0)	Analysed (n = 20) Excluded from analysis (n = 0)

Figure 1. Participation consort flow diagram

Two patients declined to participate in study and four patients refused to continue the trial. The ineffectiveness of treatment on the symptoms of illness and lack of adequate time for follow-up were mentioned as the reason for treatment refusal. Forty randomized patients completed the trial.

At the beginning of the study, all eligible patients were assessed using Visual Analog Scale (VAS), Multiple Outcomes Study (MOS) Sleep Scale, and Fibromyalgia Impact Questionnaire (FIQ). The validity and reliability of FIQ have been approved by other studies.[17] The Persian translation of this questionnaire is a valid and reliable tool for assessing the health status of Persian-speaking patients with FM.[18] The validity and reliability of MOS Sleep Scale have also been demonstrated in previous studies.[19-21]

MOS Sleep Scale measures 12 items in 6 dimensions of sleep including sleep disorder, sleep efficiency, amount of sleep, sleepiness, snoring, and shortness of breath or headache. The sessions were twice a week (each for 30 minutes) for a period of 4 weeks. Group 1 underwent SMR neurofeedback training or training on Cz sensorimotor area and group 2 underwent neurofeedback training for alpha-theta training on Pz area. Neurofeedback was performed using ProComp 2 devices and Thought Technology software in the neurofeedback unit of Imam Khomeini Hospital.

In total, 40 patients were selected and randomly assigned to two groups (block randomization). First, a number was allocated to each patient, then they were assigned into blocks of 4 patients, and finally the blocks were studied using RANDBETWEEN function of Microsoft Excel software. Study investigators, research coordinators, attending care teams, and the patients were blinded to

treatment allocation.

The primary outcomes were pain and quality of life (QOL), which were measured using VAS, Numeric Pain Scale, FIQ, and MOS Sleep Scale, respectively, at the beginning of study and at the end of eight sessions of neurofeedback (after four weeks); and four weeks after the last session of neurofeedback training were filled by patients. We estimated that a total of 40 patients would be needed to detect a difference between groups, with a two-tailed α of 0.05 and a (1-β) of 0.80, for a comparison of 2 independent proportions. Repeated measures analysis of variance (ANOVA) was used to compare the results between the two groups. P-values of less than 0.050 were regarded as statistically significant. All analyses were conducted using SPSS software (version 16, SPSS Inc., Chicago, IL, USA).

Results

Baseline demographic and clinical characteristics were similar in both groups.

The mean age of patients in group 1 (SMR neurofeedback training) was 41.64 ± 5.70 years and in group 2 (alpha-theta neurofeedback training) was 39.75 ± 5.06 years, that the difference was not statistically significant (P = 0.319). In both groups, there was statistically significant differences between the scores of VAS (pain severity) at the beginning of study, end of the fourth week, and end of the eighth week (P = 0.001). Nevertheless, using repeated measures ANOVA, there was not a statistically significant difference between the two groups (P > 0.050) (Figure 2).

The FIQ: In group 1, there was a statistically significant difference in the mean scores of FIQ at the beginning (60.07 ± 12.08) and at the end of study (44.66 ± 14.09) (P < 0.001). In group 2, there was a statistically significant difference in the mean scores of FIQ at the beginning (56.77 ± 17.24) and at the end of study (38.30 ± 17.06) (P = 0.001).
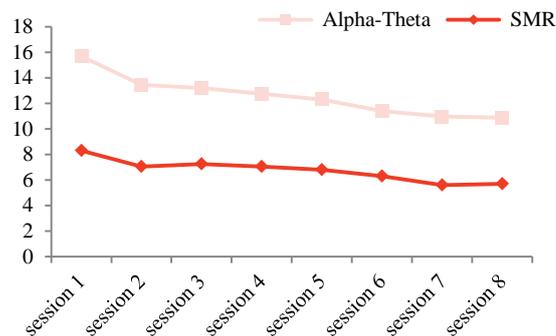

Figure 2. Visual Analog Scale (VAS) of pain during 8 sessions of neurofeedback treatment in alpha-theta and sensorimotor rhythm (SMR) neurofeedback groups

The follow-up of patients showed a higher FIQ score after eighth week compared to the fourth week; nevertheless, the difference between initial and final (8 weeks) FIQ scores was still statistically significant (P < 0.050) (Figure 3).
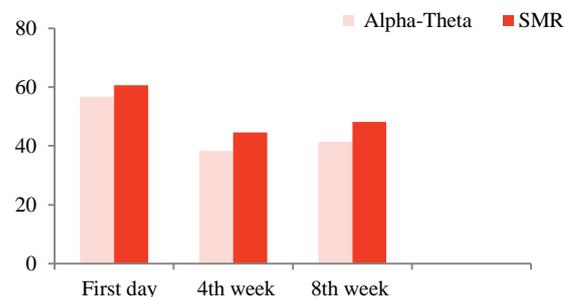

Figure 3. The Fibromyalgia Impact Questionnaire (FIQ) in alpha-theta and sensorimotor rhythm (SMR) neurofeedback groups

MOS Sleep Scale: In group 1 patients, there was a statistically significant difference between MOS scores in the beginning and at the end of the study (P < 0.050). In group 2 patients, there was a statistically significant difference between MOS scores in the beginning and end of the forth week (P < 0.050). But the difference between the two methods was not statistically significant (P > 0.050). In this study, no statistically significant difference was observed between the two treatment protocols after the eighth week (P > 0.050) (Table 1).

Table 1. Mean and standard deviation (SD) of Medical Outcomes Study (MOS) Sleep Scale in both groups

Neurofeedback protocol	1st day (mean ± SD)	4th week (mean ± SD)	8th week (mean ± SD)	P (1st day/4th week)	P (1st day/8th week)
SMR	32.05 ± 6.45	34.78 ± 5.44	32.20 ± 5.01	0.042	0.370
Alpha-theta	33.26 ± 4.02	35.68 ± 5.41	33.80 ± 4.30	0.045	0.040
P (SMR/alpha-theta)	0.590	0.580	0.682	-	-

SMR: Sensorimotor rhythm; SD: Standard deviation

Discussion

Neurofeedback facilitates inhibitory mechanisms in thalamus and can reconstruct the pain pathways in patients with FM.[22] Some studies have also supported the hypothesis that neurofeedback can increase the amplitude of the delayed P300, that this triggers the inhibitory mechanism of the thalamus. The facilitation of inhibitory mechanisms may play a positive role in the central regulation of pain and changing the central reinforcement.[23] This theory was the basis of this study for the use of neurofeedback in reducing pain in patients with FM.

Few studies have been conducted to reduce pain by neurofeedback. These studies have shown that chronic pain is reduced by this method.[24] For instance, the decrease in complex regional pain syndrome type I (CRPS-I) associated with migraine has been noted using neurofeedback method.[16] Furthermore, it has been shown that neurofeedback compared with escitalopram further improves the disease symptoms and QOL.[6] All patients in our study during a 4-week treatment with the two neurofeedback protocols, SMR and alpha-theta, sequentially mentioned lower pain intensity. As neurofeedback cannot affect the severity of symptoms immediately especially the pain, therefore, this led to the discouragement of patients to follow the treatment. The strength of our study compared to previous studies was the evaluation of two neurofeedback protocols at the same time and the comparison of the effectiveness of the two protocols including SMR reinforcement, which its effects on FM has been shown in previous studies and alpha-theta reinforcement protocol that its

effect on patients with FM has not been investigated so far.[25] Kayiran et al. conducted a randomized study but only the evaluator was blind to the intervention.[6] None of the three other studies conducted in this context had randomized double-blind design with control groups.[7,8,25] Similar to other studies, all participants in this study were women, which indicates very high prevalence of the disease among women.

In the study by Kayiran et al.,[6] patients who received neurofeedback and were not allowed to take any type of medication were compared with patients who received escitalopram. In the studies by Kravitz et al.[5] and Nelson et al.,[26] patients were allowed to take medications such as morphine, benzodiazepines, and serotonin reuptake inhibitors at the same time. But in our study, except taking pregabalin, the patients were not under treatment with any medication.

The results of this study were consistent with the results of other studies. According to our results, both neurofeedback protocols were equally effective in reducing pain and this effect was maintained for up to 4 weeks after the treatment termination. In the study by Kayiran et al., patients were treated with neurofeedback for 4 weeks. VAS tool was used to measure the pain of patients. In this study, the patients' pain was evaluated until week 24 and according to the data, pain reduction process was clearly observed until week 8 and afterwards the treatment method showed no further beneficial effect in reducing pain.[6]

In the present study, there was a statistically significant difference between FIQ scores of all patients at the beginning of the study and at

the end of the eight weeks of treatment. Similar to our results, in the study by Kayiran et al.[6], which was conducted on a smaller number of patients in a shorter period of time, the FIQ scores significantly progressed during the study.

In another study by Nelson et al., conducted on 32 patients with FM, MOS Sleep Scale and FIQ were used to assess the effect of treatment on patients. In this study, patients were divided into two groups; one group was placebo feedback group and another group was treated actively with Low Energy Neurofeedback System (LENS) neurofeedback method. In this study, the amount of MOS significantly reduced during the study, which is in line with our results. Moreover, in this study, patients were followed up twice within 3 months and 6 months after treatment.[26]

On the other hand, Kravitz et al. conducted a study on 58 patients with FM. The FIQ questionnaires were completed by the patients before and after treatment. The results showed no statistically significant difference.[5]

The results of the present study indicated that the use of alpha-theta neurofeedback, similar to SMR neurofeedback could be a suitable method in reducing pain in patients with FM and improving sleep quality and FIQ index in these patients. This result is consistent with the results of previous studies on the impact of relaxation techniques (relaxation) on decreasing pain.[25] SMR neurofeedback training methods by strengthening amplitude of waves from 12 to 15 Hz can increase attention and concentration, cognitive processing, and sleep quality and can reduce fatigue.[26] Unlike SMR training that is performed in the area of sensorimotor with open eyes, alpha-theta neurofeedback is performed with eyes closed and in a different location behind the head, and through 7 to 8 Hz reinforcement of the waves helps to induce relaxation and meditation and reduce stress and anxiety levels, and hence, demonstrates therapeutic effect.[9,26]

Conclusion

It can be said that performing any neurofeedback training protocol finally through instructing self-regulation can be effective in reducing the pain sensation and pain perception. Taken together, further studies with larger sample size and longer follow-up are recommended. In addition, the utilization of methods such as functional magnetic resonance imaging (fMRI) during the treatment is suggested to be able to more precisely examine the main mechanism of the disease and the effectiveness of treatment in patients.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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