

EFFECT OF TELEREHABILITATION BASED HIGH INTENSITY INTERVAL TRAINING ON BIOCHEMISTRY PARAMETERS AND SYMPTOMS IN PATIENTS WITH FIBROMYALGIA

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ABSTRACT

Purpose: Fibromyalgia syndrome (FMS) is a chronic musculoskeletal disease of unknown etiology accompanied by symptoms such as pain, hyperalgesia, sleep disorders, fatigue and mood disorders. The purpose of this study was to evaluate the effect of telerehabilitation-based high intensity interval training (HIIT) on blood parameters and disease symptoms in FMS.

Material and Methods: 33 fibromyalgia patients were randomly assigned as HIIT (n = 11), moderate-intensity continuous training (MICT) (n=11) and control (CG) (n=11). While the patients in the study groups were given upper extremity exercise with telerehabilitation for 6 weeks, no intervention was applied to the CG. Disease symptoms and blood parameters were evaluated before and after treatment.

Results: In the post-treatment intra-group evaluation, a significant increase was observed in the HIIT group superoxide dismutase (SOD), malondialdehyde (MDA), glutathione peroxidase (GSH-Px), pressure pain threshold, right handgrip values, while a significant decrease was detected in fatigue severity and fibromyalgia impact scores. In the MICT group, a significant decrease was observed in SOD, myeloperoxidase (MPO), fatigue severity values, while a significant increase was detected in pressure pain threshold and left handgrip values. In the inter-group evaluation, significant differences were detected in post-treatment right handgrip, fatigue severity, fibromyalgia impact score, MPO and SOD values (p<0.05).

Conclusion: HIIT may be an effective treatment choice for patients.

Keywords: Exercise; Rehabilitation; Oxidative stress

INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal disease of unknown etiology

accompanied by symptoms such as pain, hyperalgesia, sleep disorders, fatigue and mood disorders. The serotonergic system has been

associated with many symptoms such as depression, sleep problems, anxiety, fatigue, and pain. Tryptophan is the precursor to serotonin in the system (1).

Studies on FMS have reported that plasma tryptophan, serotonin and vitamin D levels (25-OH Vit D) decrease in this patient group. In the treatment of FMS, aerobic exercise reduces the amount of amino acids that compete with tryptophan by allowing the muscles to use branched-chain amino acids (BCCAs) and increases the chances of tryptophan passing the blood-brain barrier. Therefore, it has the potential to increase serotonin in the brain (2). It is stated that physical activity may be a way to achieve higher serum vitamin D levels in the population, and it is suggested that endurance exercises may increase circulating 25-OH Vit D (3).

The type of exercise given to FMS patients is important. Studies have shown that when aerobic exercises are applied regularly for a long time, the level of lipid peroxidation malondialdehyde (MDA), which is an indicator of oxidative stress, decreases and the antioxidant enzyme activity (SOD) increases (4). Studies conducted in recent years focus on high intensity interval training (HIIT). HIIT are shorter in duration compared to moderate intensity continuous training (MICT) and produce the same or more positive effects compared to MICT (5). Compared to lower extremity training, upper extremity HIIT training has received relatively less attention in studies. We thought that this form of exercise could produce beneficial results for the FMS patient group who have problems in upper extremity muscle strength and performance due to pain and physical inactivity and condition (6). During the pandemic period, studies involving video-guided exercise programs accompanied by telerehabilitation in fibromyalgia patients were reported in the literature (7).

The primary aim of this study was to evaluate the effect of telerehabilitation-based upper extremity-HIIT on biochemistry parameters and disease symptoms in FMS patients.

MATERIALS AND METHODS

This study is a prospective, randomized controlled trial with blinded assessors. Ethics committee approval for the study was obtained from the Clinical Research Ethics Committee of Bakırköy Doctor Sadi Konuk Training and Research Hospital (Date: 12.07.2021, Decision No: 2021-14-05). The study was registered on the ClinicalTrial.gov website and

the registration number is NCT05502003. The study was conducted with written informed consent from each patient and in accordance with the Declaration of Helsinki.

A total of 33 patients diagnosed with fibromyalgia at the Physical Medicine and Rehabilitation outpatient clinic of Bakırköy Sadi Konuk Research and Training Hospital participated in this study. Patients between the ages of 18-65 years who were followed up in the hospital with the diagnosis of fibromyalgia (American College of Rheumatology 2016) and agreed to participate in the study were included in the study (8). Participants were patients who had regular doctor check-ups and did not participate in any physical therapy or exercise program. All patients were invited to the study by phone call by the responsible physiotherapist. Since they were under routine control in terms of the drugs used, no changes were made. Exclusion criteria were infection, fever, contraindication to physical activity, any known advanced pathology related to the locomotor system, cardiopulmonary problem, presence of autoimmune disease, pregnancy, malignancy, severe psychiatric disorder, neurological disorder and epilepsy. Eligible patients were informed about the study and an informed consent form was filled.

Patients were assigned to HIIT, MICT, and control (CG) groups through a simple randomization technique. The participants were applied one-on-one telerehabilitation (Zoom-video conference) and upper extremity exercise program for 6 weeks/ 3 times a week, accompanied by a physiotherapist (5.9).

The upper extremity aerobic exercise program was performed with the arm ergometer provided to the participants. Pulse oximetry was used to evaluate heart rates during exercise. The exercise intensity was calculated by determining the Maximum Heart Rate (MHR) method. For HIIT, it was started with a warm-up at MHR (50%) for 5 min. The cycles were continued with high intensity at 4 min MHR (80-95%) and active recovery cycles at 3 min MHR (70%) and ended with a cooldown at 5 min MHR (50%) and the program took 35 min in total. Participants in MICT received a total of 55 min of exercise training at 65-70% of Maximum Heart Rate, following the same warm-up and cool-down period as the HIIT group. All evaluations were evaluated by the responsible physiotherapist before and after 6 weeks of treatment. Blood samples for biochemical analysis was performed by a responsible nurse. Biochemical

analyzes were completed by the responsible physician (5).

Biochemical analyzes such as MDA, myeloperoxidase (MPO), SOD, glutathione peroxidase (GSH-Px), 25-OH Vit D, free serum tryptophan, 5 hydroxyindoleacetic acid 5-HIAA were determined in the study. The all blood samples were collected in tubes and the samples were centrifuged for serum removal. The samples were centrifuged at 2000 x g for 10 min and serum samples were stored frozen at -80 °C until study data were completed. Serum concentrations of these parameters were determined with ELISA kits, using a sandwich ELISA technique (Catalogue numbers: E0880Hu for MPO, E1371Hu for MDA, E1912Hu for 5-HIAA, E0918Hu for SOD, E4244hu for tryptophan, E1981Hu for 25 OH Vit D and E0725Hu for GSH-Px). Assays were carried out according to the manufacturer's instructions. The sensitivities of each assay were 0.05 ng/ml for MPO, 0.14 nmol/ml for MDA, 9.29 ng/L for 5-HIAA, 1.52 U/L for SOD, 0.23 ug/ml for tryptophan, 0.23 ng/ml for 25 OH Vit D and 1.12 U/ml for GSH-Px (10). The inter-and intra-assay coefficients of variation were CV<10% and CV<8% and the assay range were 0.1-30 ng/ml for MPO, 0.2 nmol/ml-60 nmol/ml for MDA, 20-4500 ng/L for 5-HIAA, 3-900 U/L for SOD, 0.5-200 ug/ml for tryptophan, 0.5-150 ng/ml for 25-OH Vit D and 2-600 U/ml for GSH-Px.

Algometer (Baseline® Dolorimeter) was used on 18 tender points to evaluate the pressure pain threshold. The evaluation score was obtained by averaging the values obtained at each point. (11). Fatigue Severity Scale, was used for fatigue assessment. A low score is associated with the participant's low fatigue level (12). Hand grip strength was evaluated with a dynamometer (Jamar Hydraulic Hand Dynamometer). Patients sat in a chair with their shoulders adducted, their elbows flexed to 90°, and their forearms and wrists in a neutral position. Hand grip strength normally ranges from 30 to 50 kg, depending on age and gender (13). Psychological status was assessed with the Hospital Anxiety and Depression Scale. For anxiety and depression values, 0-7 points are considered normal, 8-10 points are borderline, and 11 points and above are considered abnormal (14). Sleep quality was assessed with the 'Pittsburgh Sleep Quality Index'. The total score in this index ranges from 0 to 21, with a higher score indicating poor sleep quality (14). Participants' functional status was assessed using the 'Revised Fibromyalgia Impact Questionnaire.' A

higher score on the questionnaire indicates that fibromyalgia affects function more (15).

Statistical analysis: Appropriate sample size was calculated based on (GSH-Px) from a similar previous study using G*Power 3.1. According to this effect size, for ANOVA: Fixed Effects, omnibus, one-way test analysis, with 95% power and $\alpha=0.05$, a total of 33 people, 11 people to each group, should be taken (16-17). For continuous variables, one way ANOVA and Tukey's Post Hoc Test were used. Kruskal Wallis test and Wilcoxon signed rank test were used for nonparametric variables.

RESULTS

There were no statistically significant differences between the descriptive data of the groups shown in Table 1.

Table 1. Characteristics of participants

	HIIT (n=11)	MICT (n=11)	CG (n=11)	P
Age (y), mean (SD)	46.82 (9.66)	46.45 (9.12)	51.36 (8.73)	0.38
Gender (M:F), n	1:10	1:10	1:10	1.00
Body mass index (kg/cm ²), mean (SD)	30.29 (6.01)	27.85 (4.11)	27.01 (4.79)	0.30

HIIT= high intensity interval training group, MICT= Moderate intensity continuous training group, CG= Control group, BMI= Body mass index. $p<0.05$

As a result of the post-study actual power analysis, the study power was determined as 0.78. When the post-treatment biochemical values of the groups were compared, given in Table 2, a significant difference was detected in SOD and MPO values. The significant difference in SOD values is due to the increase in SOD in the HIIT group and the decrease in SOD in the MICT group. The difference in MPO values is also due to the HIIT group. When the intra-group changes before and after treatment were examined, significant changes were found in SOD, MDA, GSH-Px for HIIT, and SOD and MPO values for MICT. The effect of treatment on symptoms is shown in Table 3. In the comparison between the groups after the treatment, a significant difference was found between the groups' right grip strength and fatigue values, and it was determined that this difference was caused by HIIT and CG. When the changes within the group were examined, a significant improvement was found in the pressure pain threshold, right grip and fatigue severity values in the HIIT group, and in the left grip and fatigue severity values in the MICT group ($p<0.05$).

Table 2. Intra- and intergroup effect of treatment on biochemical parameters

Outcomes	Group	Time period		p*	p** (before)	p** (after)
		Baseline	6 weeks			
Free Trp (ug/ml)	HIIT	15.5(7.9-73.6)	12.3(8.9-63.8)	0.15	0.03	0.72
	MICT	10.6(3.8-16.4)	12.1(2.8-14)	0.18		
	CG	11.1(7.5-26.1)	12.1 (6.6-28.4)	0.45		
5-HIAA(ng/L)	HIIT	437(-163-1487)	207(-13-1597)	0.59	0.40	0.37
	MICT	160(53.6-313.6)	153.6(-43-477)	0.72		
	CG	157(73.6-370.3)	207(107-463.6)	0.24		
SOD (U/L)	HIIT	79.9(37.6)-275.2)	109.1(63.2-314)	0.008	0.69	0.003
	MICT	75.9(39.9-105.8)	60.0(1.02-82.9)	0.02		
	CG	76.2(16.2-104.2)	71.5(56.9-335.4)	0.24		
MDA (nmol/ml)	HIIT	10.19(6.1-26.8)	10.2(7.5-36.2)	0.004	0.25	0.067
	MICT	8.21(5.2-11.05)	8.71(4.2-12.6)	0.37		
	CG	8.97(6.3-14.8)	9.46(6.2-16.9)	0.72		
25-OH Vit D(ng/ml)	HIIT	6.83(1.4-39.7)	7.36(4.7-39.8)	0.53	0.02	0.07
	MICT	5.12(0.5-9.5)	6.13(2.93-7.36)	0.21		
	CG	4.8(2.6-11.4)	5.22(2.6-12.8)	0.53		
MPO (ng/ml)	HIIT	2.98(1.3-8.6)	3.28(1.9-8.2)	0.21	0.08	0.03
	MICT	2.23(0.4-3.4)	1.97(0.3-3.2)	0.02		
	CG	2.12(1.4-4)	2.14(0.2-3.9)	0.20		
GSH(PX) (U/ml)	HIIT	17.73(1.0-107.7)	17.93(8.5-127.1)	0.01	0.18	0.11
	MICT	13.29(1.0-28.3)	12.58(1-27.6)	0.59		
	CG	17.86(1.0-33.7)	16.52(3.8-32.6)	0.47		

*Wilcoxon signed rank test. ** Kruskal Wallis test. HIIT= high intensity interval training group, MICT= moderate intensity continuous training group, CG= control group, SOD= Superoxide dismutase, MDA= Malondialdehyde, GSH-Px= Glutathione peroxidase, MPO= Myeloperoxidase, 5-HIAA= 5-Hydroxyindoleacetic acid, Trp= Tryptophan, OH= Hydroxide, Vit= Vitamin. p<0.05.

Table 3. Intra- and intergroup effect of treatment on symptoms

Outcomes	Groups	Time period		p*	p** (before)	p** (after)
		Baseline	6 weeks			
Pressure pain threshold	HIIT	4.71±0.85	5.48±1.5	0.003	0.72	0.49
	MICT	4.82±1.53	5.20±1.49	0.009		
	CG	5.10±1.05	4.77±1.12	0.03		
Handgrip strength-R (kg)	HIIT	43.18±7.83	45±7.41	0.038	0.08	0.034
	MICT	38.64±10.02	38.18±10.55	0.341		
	CG	35.45±4.71	35.91±5.39	0.676		
Handgrip strength-L (kg)	HIIT	35.91±14.97	37.73±12.91	0.10	0.16	0.33
	MICT	27.73±7.86	31.36±10.51	0.03		
	CG	33.64±5.04	34.09±4.36	0.72		
Fatigue FSS (0-7)	HIIT	5.64±1.19	4.96±1.15	0.004	0.41	0.031
	MICT	6.30±0.74	5.84±0.82	0.016		
	CG	6.02±1.38	6.12±1.02	0.472		
Sleep quality PSQI (0-21)	HIIT	7.64±2.76	7.82±2.71	0.34	0.47	0.53
	MICT	8.91±4.39	8.64±4.36	0.19		
	CG	9.36±2.76	9.45±2.77	0.34		
HADS-Anxiety (0-21)	HIIT	7.82±4.07	7±3.60	0.28	0.38	0.19
	MICT	9.64±4.88	8.82±5.03	0.09		
	CG	10.45±4.56	10.55±4.61	0.341		
HADS-Depression (0-21)	HIIT	4.36±3.72	4.09±3.72	0.19	0.50	0.53
	MICT	5.82±3.99	5.45±4.18	0.45		
	CG	6.27±4.17	6.64±4.03	0.16		
RFIQ (0-100)	HIIT	51.91±14.30	46.45±14.83	0.006	0.24	0.02
	MICT	53.18±12.06	50.73±12.14	0.13		
	CG	60.23±9.63	64.45±9.20	0.19		

*Paired Sample T Test, **One Way ANOVA. HIIT= high intensity interval training group, MICT= moderate intensity continuous training group, CG= control group, FSS= Fatigue Severity Scale, PSQI= Pittsburgh Sleep Quality Index, HADS= The Hospital Anxiety and Depression Scale, RFIQ= Revised Fibromyalgia Impact Questionnaire, R: right, L: left. p<0.05

DISCUSSION

We think that this study we have conducted is the first randomized controlled study to examine the effects of telerehabilitation-based HIIT on biochemical parameters in FMS patients. A study on lower extremity-based HIIT was also conducted by Atan et al. in 2020 in the FMS patient group, but biochemical parameters were not evaluated in this study. In a study evaluating the effect of exercise on 5-HIAA levels, the effect of 20-week aerobic exercise and stretching exercise programs on serotonin metabolites was evaluated, and a significant increase was found in the 5-HIAA levels of the aerobic exercise group. In a study evaluating the effects of different exercise intensities on vitamin D levels, the effects of HIIT on serum vitamin D levels in obese male adolescents were evaluated. Although it has been determined that the 8-week HIIT program improves vitamin D levels in adolescent men, it has been reported that further studies in different age ranges are needed. In the results of our biochemical analysis, no statistically significant difference was observed regarding the serotonergic system and vitamin D, but there were significant differences in oxidative stress in the exercise groups. (5,18).

Oxidative stress is very important in the pathophysiology of FMS. Under normal conditions, regular exercise reduces the level of MDA, which is a sign of oxidative stress, and increases the level of SOD. SOD and GSH-Px constitute the basic line of defense against free radicals in the cell. In the event of excessive exercise, a great increase in oxygen consumption leads to oxidative stress. In our study, in the HIIT group, exercise increased SOD, GSH-Px and MDA after treatment, leading to an increase in both oxidative stress and the antioxidant mechanism that constitutes the primary line of defense. However, MPO levels showed a significant improvement only in the MICT group, but SOD levels showed a significant decrease in this group. Recent studies have reported that oxidative stress plays a role in the pathophysiology of fibromyalgia and that lipid peroxidation products caused by oxidative stress increase in the plasma of patients. It has also been stated that the antioxidant capacity of these patient groups decreases. The reason for the decrease in SOD levels may be related to this situation (19,20,21).

Fatigue, along with pain and sensitivity, is one of the most important symptoms that negatively affect the daily life and psychological state of fibromyalgia

patients. In a systematic review evaluating the effect of exercise on fatigue severity in fibromyalgia patients, it was determined that exercise was moderately effective in reducing fatigue. In our study, the effect of aerobic exercise groups on fatigue was found to be significant, while the effect values were higher in the HIIT group. Fatigue severity decreased in all exercise groups, supporting the literature. The fact that the effect size of the HIIT group was higher supports the literature (22).

Publications have reported a decrease in grip strength, especially in fibromyalgia patients. In our study, it was determined that the participants had a grip strength of 30-50 kg, which is expected in the healthy group. However, since it is dominant, it is an expected result that the right grip strength values are higher than the left. In the HIIT group, there was a significant increase in the right hand grip strength and in the MICT group in the left hand grip strength. It is known that factors such as pain intensity, depression, and sleep quality in fibromyalgia can affect a person's grip strength. For this reason, we think that we obtained different results in two separate exercise groups (23).

In relation to the revised fibromyalgia impact questionnaire, different exercise programs have been reported to improve symptoms and provide significant reductions in survey results. Due to the significant improvements in symptoms in our study, the improvements seen in the Revise Fibromyalgia Impact Questionnaire in the HIIT group are expected. Although improvements were observed in parameters such as fatigue and grip strength in the MICT group, the HIIT group developed more significant results. The fact that no significant change was observed in depression, anxiety and sleep quality in our study may be attributed to the fact that FMS is a complex disease and is related to factors such as patients' sleep status and family life.

Telerehabilitation is a widely used approach in treatment processes, especially during the pandemic period. In a study evaluating the acute effects of telerehabilitation and aerobic exercise on the symptoms of the disease in female patients with FMS, significant results were reported especially for pain symptoms. Obtaining similar results with exercise programs and face-to-face treatment programs on many symptoms in our study results is a finding that supports the effectiveness of telerehabilitation and exercise (8).

It is possible to report many limitations in the treatment process. Patients have been using drugs for a long time. They continued to use drugs during the treatment process, but a new drug was not started and the existing drug dose was not changed in order not to affect the treatment results. Another limitation is that we did not clearly assess the physical activity levels in the CG. Patients may have been involved in aerobic exercise activities such as walking and swimming, aerobic exercise is definitely recommended for this patient group. For this reason, it is not possible to restrict aerobic activity. Another shortcoming is that the evaluating therapist is not blind.

CONCLUSION

In a patient group such as FMS, where exercise is recommended as a treatment option without side effects with strong evidence, telerehabilitation-based exercise training both reduces contact and allows patients to complete their exercise processes without disrupting their daily lives. HIIT training can be considered as an effective treatment method because it produces similar results to MICT and requires a shorter treatment time. However, longer-term exercise studies are needed for symptom control and blood analysis.

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Conflict of Interests: All authors declare that there is no conflict of interest.

Ethics Approval: The study was approved by Clinical Research Ethics Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Date: 12.07.2021, Decision No: 2021-14-05, Protocol Number: 2021/364). All participants gave written informed consent before data collection began. Clinical trial registration number: ClinicalTrials.gov: NCT05502003.

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