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ORIGINAL ARTICLE

Randomized, blinded, controlled trial on effectiveness of photobiomodulation therapy and exercise training in the fibromyalgia treatment

Mariana Moreira da Silva[1] · Regiane Albertini[2] · Paulo de Tarso Camillo de Carvalho[1] · Ernesto Cesar Pinto Leal-Junior[1] · Sandra Kalil Bussadori[1] · Stella Sousa Vieira[2] · Danilo Sales Bocalini[3] · Luis Vicente Franco de Oliveira[4] · Vanessa Grandinetti[1] · José Antonio Silva Jr[1] · Andrey Jorge Serra[1]

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Abstract This study evaluated the role of the phototherapy and exercise training (EXT) as well as the combined treatment in general symptoms, pain, and quality of life in women suffering from fibromyalgia (FM). A total of 160 women were enrolled and measures were carried out in two sets: it was sought to identify the acute effect for a single phototherapy and EXT session (*Set 1*); long-term effect (10 weeks) of the interventions (*Set 2*). Phototherapy irradiation was performed at 11 locations in their bodies, employing a cluster with nine diodes (one super-pulsed infrared 905 nm, four light-emitting diodes [LEDs] of 640 nm, and four LEDs of 875 nm, 39.3 J per location). Algometry and VAS instrument were applied to evaluate pain. The FM symptoms were evaluated with Fibromyalgia Impact Questionnaire (FIQ) and Research Diagnostic Criteria (RDC) instruments. Quality of life was assessed through SF-36 survey. *Set 1*: pain threshold was improved with the phototherapy, and EXT improved the pain threshold for temporomandibular joint (right and left body side) and occipital site (right body side). *Set 2*: there was improved pain threshold in several tender points with the phototherapy and EXT. There was an overlap of therapies to reduce the tender point numbers, anxiety, depression, fatigue, sleep, and difficulty sleeping on FIQ/RDC scores. Moreover, quality of life was improved with both therapies. The phototherapy and EXT improved the pain threshold in FM women. A more substantial effect was noticed for the combined therapy, in which pain relief was accomplished by improving VAS and FIQ scores as well as quality of life.

Keywords Exercise training · Fibromyalgia · Quality of life · Pain · Phototherapy

Introduction

Fibromyalgia (FM) is a non-inflammatory syndrome usually manifested in women, in which it is associated with widespread chronic pain, sleeping disorder, fatigue, morning stiffness, paresthesias, and anxiety, impaired cognition as well as quality of life [1, 2].

The main targets in FM treatment are pain control and improve functional capacity, which can be fulfilled using a variety of pharmacological interventions. If patients do not tolerate the drugs or if additional symptoms relief is necessary to keep the functionality, other treatments might be necessary. Moreover, patients frequently use alternative therapies, indicating frustration or drug therapy unsuccessfulness. Thus, this information is consistent with the need of new therapies, especially nonpharmacological one [2, 3].

As an additional intervention, there is evidence for a beneficial role of the exercise training (EXT) in FM patients. It was shown in this study that exercise training can decrease pain and improve health-related quality of life as well as functional capacity [4, 5]. Another interesting development in the field of nonpharmacological intervention is the phototherapy [6]. A placebo-controlled, randomized clinical trial was carried out to evaluate low-level laser therapy (LLLT) effects in FM patients. After follow-up treatment, the number of tender

✉ Andrey Jorge Serra
andreyserra@gmail.com

[1] Laboratory of Biophotonic, Nove de Julho University, São Paulo, SP, Brazil

[2] Federal University of São Paulo, São Paulo, SP, Brazil

[3] Translational Physiology Laboratory, São Judas Tadeu University, São Paulo, SP, Brazil

[4] Centro Universitário de Anápolis, Goiânia, GO, Brazil

points as well as several FM symptoms showed significant improvements [7].

The studies above are encouraging to expect a favorable effect of EXT and LLLT as additional interventions to reduce chronic pain in patients with FM. This study was carried out to evaluate the role of the phototherapy and EXT as well as combined treatment in overall symptoms, pain, and quality of life of FM patients. Recently, light-emitting diode (LED) therapy has been used for the same purposes that LLLT and has confirmed similar results [6]. However, a review of the literature has revealed no studies involving the use of different light sources (LLLT/LED) on the same device in FM patients. Thus, a commercially available phototherapy device was used with combined LLLT/LED to facilitate the clinical application of results.

Methods

Study design and sample

The study was designed to address two main issues: (*Set 1*) it was guided to investigate immediate effect for a single session of phototherapy/EX in chronic pain condition; (*Set 2*) experiments were carried out to analyze long-term effect of the interventions (10 weeks) in the chronic pain condition and other FM symptoms. *Set 1* and *Set 2* were distinct experiments and performed with independent volunteers. Research was based on eligible patients from the three rheumatological centers. Eligible patients were evaluated for medical history, physical examination, and rheumatologic screening. Moreover, patients were applied an FM diagnostic as reported by the American College of Rheumatology on Fibromyalgia Impact Questionnaire (FIQ) [2]. The Research Diagnostic Criteria (RDC) was applied aiming at sleeping-disturbed parameters [8, 9]. Figure 1 illustrates the design scheme and participation flow through the study. The recruitment period was from November 2014 to September 2016. The ethical committee approved the study protocol (number: 419.828/2013). The study was carried out according to Declaration of Helsinki and was registered in the ClinicalTrials.gov.

The sample size was defined as recently reported by our group [6]. The inclusion criteria were women ≥ 35 years old, 5 years for FM diagnosis, optimized drug management, functionally and cognitive independence, full availability for study protocol, and no contraindication to exercise or/and phototherapy. Exclusion criteria were patients with contraindication to exercise or/and phototherapy, missing more than three treatment sessions, psychiatric disorders, missing teeth or use of dentures, history for face trauma or currently undergoing orthodontic intervention, and presence of any disorder that was confused with FM. Patients were followed through their regular health checkups, and drug therapy was continued until the end of the study. The eligible participants were tutored not to change their lifestyles or pharmacological therapies during the study. A detailed overview of the general characteristics of the patients is shown in Table 1.

A total of 160 patients were eligible for the study, in which half of these patients were randomly designated to participate in the experimental Set 1, and the other participants were guided to Set 2. Afterwards, patients were randomly assigned to one of the following groups: control (CON): patients only under pharmacological treatment; phototherapy (PHO): patients submitted to phototherapy; exercise training (EXT): patients submitted to exercise training and phototherapy placebo; (phototherapy device was turned off as a blinding procedure); phototherapy and exercise training (PHO + EXT).

Randomization procedure was performed by an independent researcher, in which each patient was coded and placed inside a dark box. Thus, the patient was sent to any of the experimental groups.

Blinding procedure and interventions

An independent researcher was responsible for programming the phototherapy device, which was turned on (phototherapy)/off (placebo) prior application. A second researcher guided the exercise training and was blinded for phototherapy and/or placebo procedure. A third researcher was blinded to the allocation of patients and independently assessed the outcomes. The statistical analysis was performed by a fourth researcher, who was blinded to experimental groups. All patients were blinded to whether the laser device was in the on or off mode.

The follow-up intervention was 10 weeks, when patients underwent two treatment sessions for phototherapy, exercise, phototherapy/exercise ,and placebo procedure per week, respectively (experimental *Set 2*). Phototherapy was applied 30 min prior to each exercise session or placebo procedure, and treatment sessions were carried out on Tuesdays and Thursdays. The outcome parameters were evaluated at baseline (prior group randomization) and 48 h after the last day of intervention. Similar intervention route was implemented to *Set 1* design; however, only a phototherapy and/or an exercise session was conducted to analyze the impact on pain. These patients were evaluated at baseline and after 24 h.

Phototherapy

The multiple light sources (LLLT and LED) Pain Away/PainCure™ nine-diode cluster device (Multi Radiance Medical®, Solon, OH, USA) was applied on 10 tender points, which were reported for pain in all patients (occipital, cervical (near the C7), trapezius, supraspinatus, second costochondral joint, lateral epicondyle, gluteal/sacrum, greater trochanter, and medial knee border). The temporomandibular joint (TMJ, bilaterally) was also

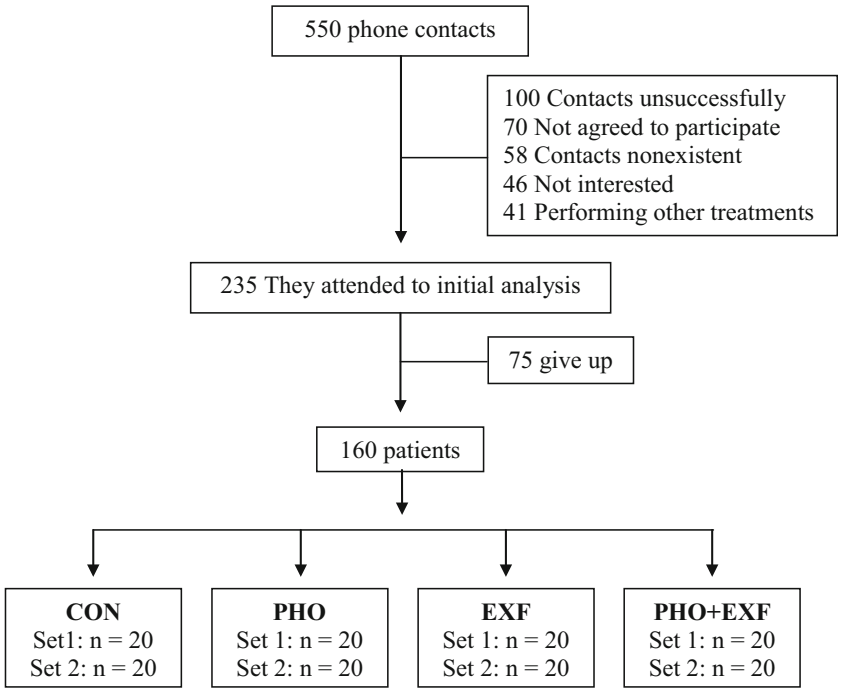

Fig. 1 Flowchart for patients included in the study

irradiated. Each point was irradiated for 300 s, and a 39.3-J total energy was delivered. Phototherapy device properties are shown in Table 2. An independent assistant controlled the phototherapy device for on/off mode because therapists and patients were blinded for the procedure.

Exercise training protocol

The EXT consisted of stretching and aerobic exercise, twice a week, over 10 weeks. Active static stretching was carried out to induce mild discomfort in the following muscle groups: biceps, trapezius, latissimus dorsi, pectoralis, paraspinal, hamstrings, and quadriceps. Each stretching exercise was performed for three times of 30 s with a 30-s rest between each stretching, which shows to be a common rest interval for stretching exercises [10]. The TMJ exercises were performed as previously reported in details [6]. Aerobic training was performed 30 min per session on motor drive movement (model LX-150) without inclination. The load exercise was 75% of age-predicted maximum heart rate (220-age (years)). Aerobic training was carried out on the bases of findings of improving the general symptoms, pain, and quality of life in women with fibromyalgia [11]. Each aerobic exercise session was started immediately after the TMJ exercises.

Outcome measures

General parameters General parameters are age, body weight, body mass index, race, educational level, employment, income, marital status, and tender point count.

Overall clinical parameters FIQ was a self-administered instrument to measure anxiety, depression, stiffness, and fatigue [9]. The RDC is a biaxial analytic tool composed of a clinical anamnesis and was carried out to determine sleeping disturbance, night awakenings, trouble sleeping, and mouth opening pattern.

Pain-related outcome

The pain threshold was analyzed with a digital algometer Instrutherm (DD-200 model). The device was placed on specific FM tender points and TMA joints using the rubber tip measuring 1 cm^2 in contact with the skin. A gradual pressure was applied until the patient reported feeling pain, and the displayed values were then recorded. The processes were executed only once to each point, and a 30-s interval was given among the readings. Moreover, visual analog scale (VAS) consisting of a 10-cm rule was applied [6].

Quality of life

Parameters were evaluated by a validated Brazilian version of the Medical Outcome study 36-item Short-Form Health Survey (SF-36) [12]. The following domains were assessed: physical functioning, role-emotional, role-physical, social functioning, mental health, vitality, and general health. The score ranges from 0 to 100, where higher score represents a better quality of life.

Table 1 Demographic characteristics and drug treatment

	Set 1	*Set 2*
Age (years)	35 ± 3	40 ± 2
Height (m)	1.58 ± 1	1.59 ± 1
IMC (kg/m^2)	26 ± 5	27 ± 4
Race	*n*	*n*
Other or biracial	48	41
White	32	39
Scholarity	*n*	*n*
Elementary School	14	9
High School	66	71
Employment	*n*	*n*
Employment or self-employment	52	50
Not employment	28	20
Income (R$/year)	*n*	*n*
< 10.000	9	4
10.000–30.000	67	75
30.000–50.000	4	2
Drug class	*Sample to two set studies*	
Analgesics		
Paracetamol	109	
Anti-inflammatory		
Amitriptilina	62	
Fluoxetina	30	
Citalopram	12	
Paroxetina	8	
Duloxetina	58	
Muscle relaxants		
Ciclobenzaprina	89	
Tizanidina	23	
Carisoprodol	5	
Hypnotics		
Benzadiazepínicos	27	

Table 2 Phototherapy parameters

Number of lasers	*1 super-pulsed infrared*
Wavelength of lasers (nm)	905
Frequency (Hz)	1000
Average optical output (mW)	0.9
Power density (mW/cm^2)	2.25
Peak power (W)	8.5
Dose (J)	0.3
Energy density (J/cm^2)	0.75
Spot size of laser (cm^2)	0.4
Number of LEDs	*4 red*
Wavelength of LEDs (nm)	640 (± 10)
Frequency (Hz)	2
Average optical output (mW)—each	15
Power density (mW/cm^2)—each	16.66
Dose (J)—each	4.5
Energy density (J/cm^2)—each	5
Spot size of LED (cm^2)—each	0.9
Number of LEDs	*4 infrared*
Wavelength of LEDs (nm)	875 (± 10)
Frequency (Hz)	16
Average optical output (mW)—each	17.5
Power density (mW/cm^2)—each	19.44
Dose (J)—each	5.25
Energy density (J/cm^2)—each	5.83
Spot size (cm^2)—each	0.9
Magnetic field (mT)	35
Treatment time (s)	300
Aperture of device (cm^2)	4
Total delivered energy per site (J)	39.3

Analysis

Data were analyzed with SPSS software, version 13.0 (Chicago, IL, USA). Shapiro Wilk was carried out to determine data distribution. Comparisons among the groups were based on analysis of the magnitude of change from the baseline to the end of the interventions (Δ%). The comparisons were analyzed by the Kruskal-Wallis test and post hoc analysis by the Dunn test. The choice of test was established on basis of data distribution.

Results

Patients' baseline characteristics are shown in Table 1, with no differences among the groups at baseline in age or anthropometric data. The patients were from different ethnicities and had the high school as their educational level; they were either employed or self-employed and they had an annual family income between 10.000 and 30.000 U$ a year. The selected patients had FM diagnosis for an average of 5 ± 9 years. All participants reported to have maintained the usual pharmacological therapy. Most of the patients used different doses of paracetamol or amitriptyline, and hypnotics were the least used pharmacological class. There were no dropouts or exclusions following randomization nor any harm or unintended outcomes reported.

Set 1 experimental results are shown in Fig. 2. The pain threshold level was improved in the PHO group, with a mean difference (Δ%) in all tender points compared to CON group. There was no significant improvement in the pain threshold after an exercise session, except for cervical C7 region of the left body side. Figure 2 also illustrates that there was no acute overlap effect of phototherapy and exercise on pain threshold. *Set 2* data are seen in Fig. 3, in which PHO group showed similar results to those reported in *Set 1*. Except for cervical

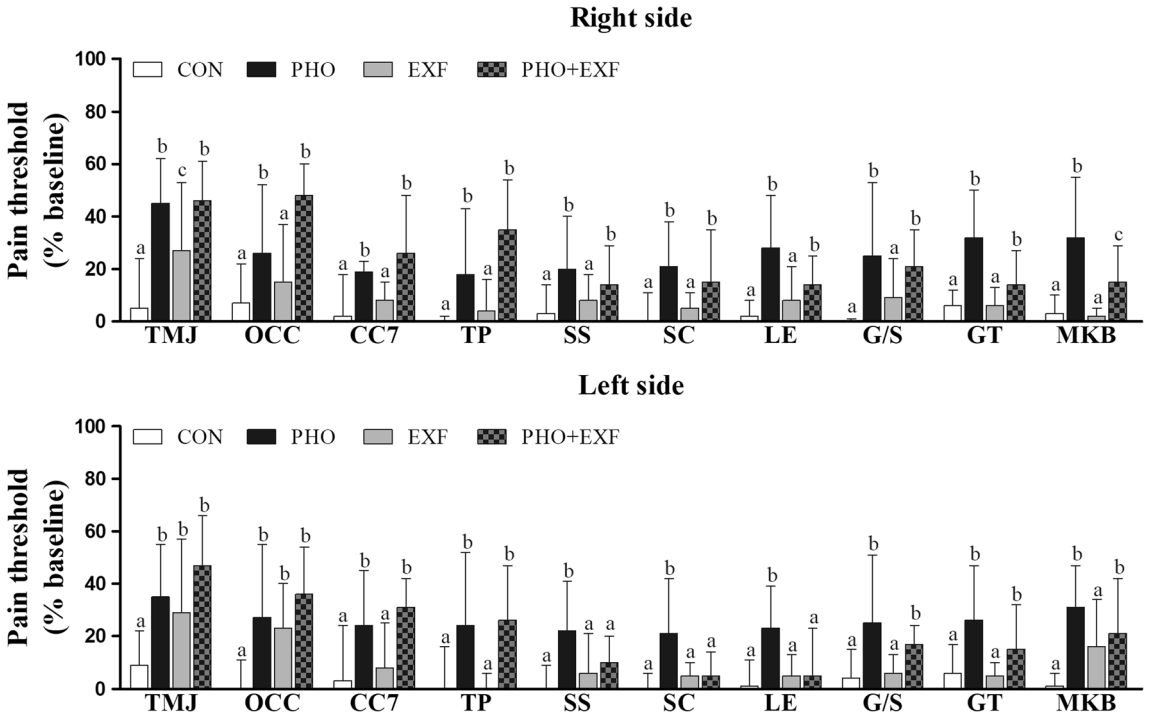

Fig. 2 Effect of a phototherapy and exercise section on pain threshold. Kruskal-Wallis test (post hoc Dunn) was applied in analysis. Different letters show significant differences among groups. Similar letters show no significant differences. Data are expressed as Δ%

and supraspinatus sites on the right body side and occipital and lateral epicondyle on the left body side, phototherapy improved the Δ% of pain threshold, with a mean difference compared to the CON group. In a different way to that observed in the *Set 1*, the data concerning the EXT group revealed improved pain threshold in several locations of the body. As depicted in Fig. 3, there were significant differences between EXT and CON in the Δ% values of right (points:

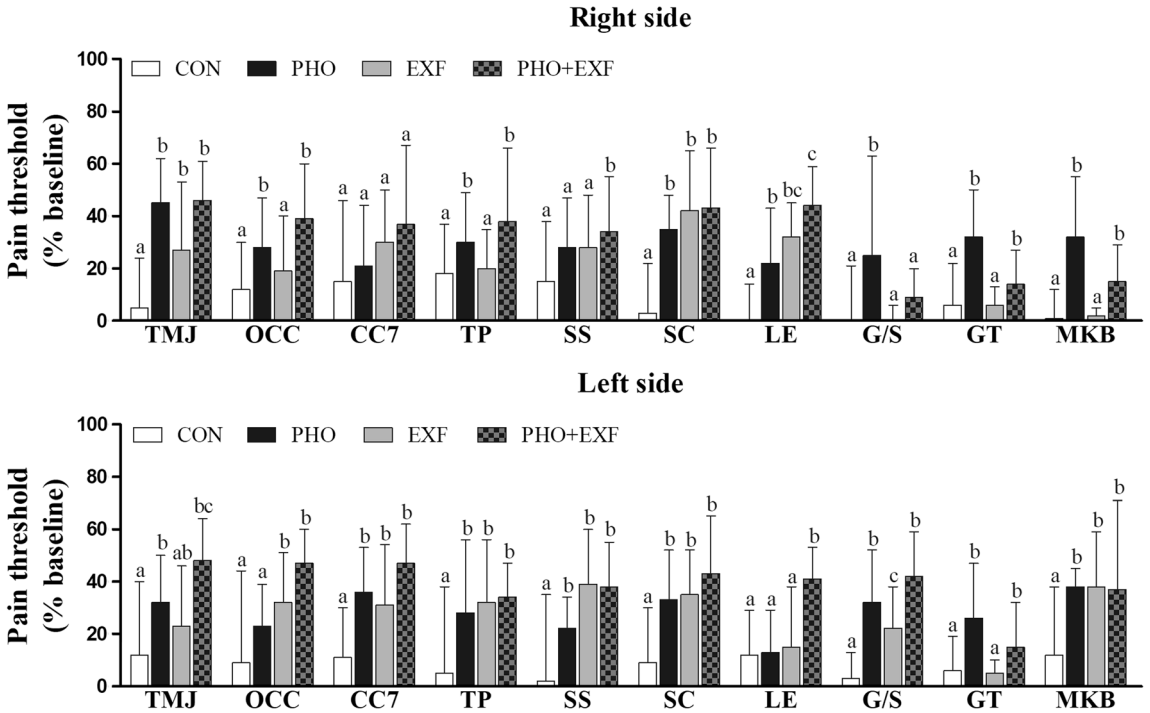

Fig. 3 Long-term effect of phototherapy and exercise training on pain threshold. Kruskal-Wallis test (post hoc Dunn) was applied in analysis. Different letters show significant differences among groups. Similar letters show no significant differences. Data are expressed as Δ%

TMJ; occipital; second condrocostal; lateral epicondyle) and left (points: occipital; cervical C7; trapezius; supraspinatus; second condrocostal; gluteal; medial knee border) body sides for the pain threshold. In the same way in the *Set 1*, no additional benefits were detected of the combination of phototherapy and exercise.

VAS was used to determine the pain perception in patients undergoing different interventions in Set 2 (Fig. 4). A large effect of phototherapy and exercise was observed, considering the post-treatment pain threshold change. It should be mentioned the superior effect of phototherapy, in which both PHO and PHO + EXT groups showed significantly greater pain reduction compared to CON and EXT groups, respectively. Another finding in Fig. 4 refers to the importance of the combined therapy to reduce the number of tender points. Thus, both PHO and EXT groups differed significantly from the CON group, a situation that was intensified in the combined therapy group.

Figure 5 summarizes overall clinical outcomes that were analyzed in *Set 2*. The combined therapies proved to be more effective, in which all the FIQ scores were significantly improved in the group PHO + EXT at the end of follow-up. Except for the "stiffness" variable in the EXT group, all values of Δ% were significantly higher in groups PHO, EXT, and PHO + EXT when compared to the CON group. Importantly, the beneficial role of combined therapy (Δ%) for anxiety, depression, and fatigue was significantly different in the PHO + EXT group compared to the other groups. Moreover, no significant differences were observed after pharmacological treatment on sleep quality markers and range of mouth opening (TMJ dysfunction marker associated to FM) in the CON group. Although the PHO group has shown a significant difference in the sleeping score and EXT group in the sleeping score and mouth opening, greater results were observed in the PHO + EXT, whereas significant differences were found in both variables and in difficulty falling sleep score. It is worth highlighting the comparisons among the groups in relation to Δ%: all parameters related to RDC exhibited values significantly superior in the PHO, EXT, and PHO + EXT compared to CON group. Furthermore, there was an additional effect of the combined therapy in sleeping and difficulty sleeping scores, whose values of Δ% were significantly higher in PHO + EXT than all the other groups.

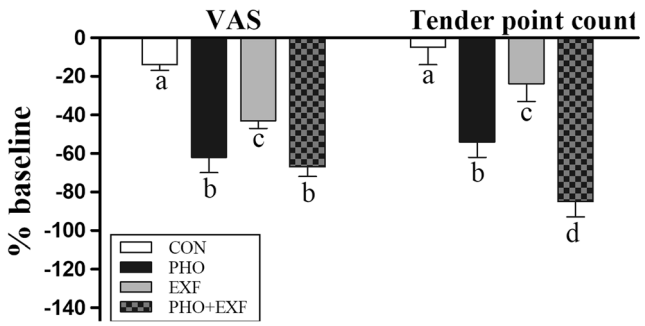

Fig. 4 Long-term effect of phototherapy and exercise training on VAS scores and tender point numbers. Kruskal-Wallis test (post hoc Dunn) was applied in analysis. Different letters show significant differences among groups. Similar letters show no significant differences. Data are expressed as Δ%

As shown in Fig. 6, it was verified that the physical functioning, role-emotional, role-physical, and vitality were significantly higher in the PHO group compared to CON group. A similar finding was noticed in the EXT group, in which physical functioning, role-emotional, role-physical, and social functioning domains were improved in comparison with CON group. A higher benefit was derived from the combined therapy—role-physical, vitality, and general health domains were potentialized (Δ%) in the PHO-EXF group.

Discussion

The purpose of the present study was to evaluate the acute and chronic repercussions of phototherapy and EXT on the pain sensitivity and quality of life of FM patients. To accomplish this objective, the pain threshold level and a variety of associated symptoms and quality of life domains were analyzed.

A real FM marker shows to be a lower pain threshold and higher pain ratings in response to several painful stimuli [12, 13]. Our data corroborate previous demonstrations that an acute exercise session has no noticeable impact on pain of patients with chronic pain [14]. As shown in Fig. 2, pressure-pain thresholds did not change from pre-exercise to post exercise, in which the exercise only showed to increase pain threshold (Δ%) for TMJ and occipital sites when compared to the CON group. It is observed that the characteristics of our exercise training were quite different from those of other studies showing increased sensitivity to exercise-induced pain [12, 15]. In fact, a major effect was prominent with long-term exercise training, in which the pain threshold under eight-point tracts was significantly increased (Fig. 3). These findings are well aligned with the data showing benefits of EXT in the FM treatment as an approach to reduce pain and to avoid disability [4, 16]. Several theories have been raised to explain how EXT reduces pain. These include increases in endogenous opioids, cannabinoids and stress hormones, conditioned pain (e.g., pain in one site may inhibit pain in another site), and attentional modulation of pain [17].

Previous studies have considered phototherapy with low-level laser therapy (LLLT) and light-emitting diode (LED) therapy as an interesting alternative to drugs in treatments of pain associated with musculoskeletal disorders. In this regard, Leal-Junior et al. [18] performed a randomized, placebo-controlled, double-blinded clinical trial to evaluate the role of phototherapy (905-nm super-pulsed laser and 875-nm infrared

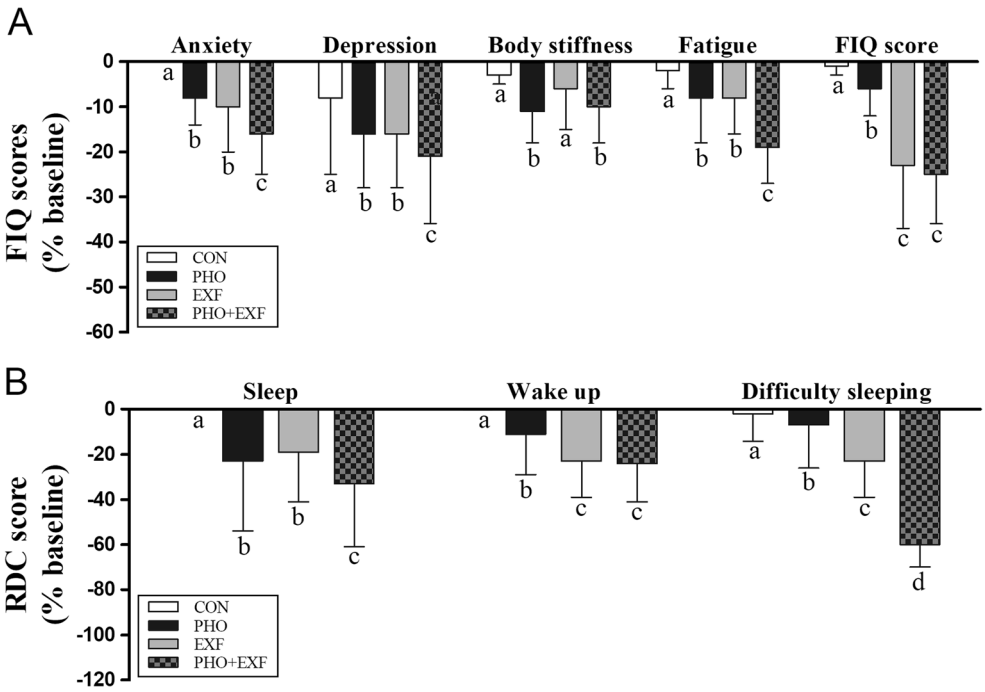

Fig. 5 Long-term effect of phototherapy and exercise training on FIQ and RDC scores. Kruskal-Wallis test (post hoc Dunn) was applied in analysis. Different letters show significant differences among groups. Similar letters show no significant differences. Data are expressed as Δ%

and 640-nm LEDs) on nonspecific knee pain. The authors showed decreased knee pain and improved quality of life with 12 treatments over 4 weeks of phototherapy. Interestingly, the beneficial role of phototherapy was sustained at 1 month of intervention discontinuation. Recently, a clinical trial provided evidence that phototherapy with super-pulsed laser (905 nm), red (640 nm), and infrared (875 nm) light-emitting diodes in the same equipment cause pain improvement in masseter and temporal muscles of women with temporomandibular disorder [19].

Our study also indicates that the combination of super-pulsed laser and visible red and infrared LED therapy can significantly improve pain ratings in FM women. Several pain tender points were improved with irradiations, with a more pronounced effect because of the chronic intervention. By stimulating multiple tender points, it is suggested that long-term clinical outcomes may be further improved with phototherapy. There is no evidence in the literature to support the use of a gold-standard dose of LLLT or LEDT against FM, due mainly to lack of studies. However, the doses employed in the research herein are similar recommendations by the World Association of Laser Therapy (WALT) [20]. In addition, the cluster device with different light sources may be a more usual phototherapeutic model because it leads to different effects and energy absorption rates [19]. Notwithstanding, the distinct wavelengths of cluster could ensure absorption of the incident photons in the chromophores as well as at the depths at which these chromophores exist [21]. Several mechanisms are hypothesized for the phototherapy to improve sensitivity pain; e.g., increased nociceptive threshold, resulting in neural blockade [22]. Moreover, an increased endorphin production and downstream opioid-receptor are linked to LLLT irradiation [22, 23]. It has also been reported that LLLT has anti-inflammatory and anti-edematous role due to the decrease of prostaglandin. On this issue, the prostacyclin ablation has been considered to provide pain regression [24, 25]. Lastly,

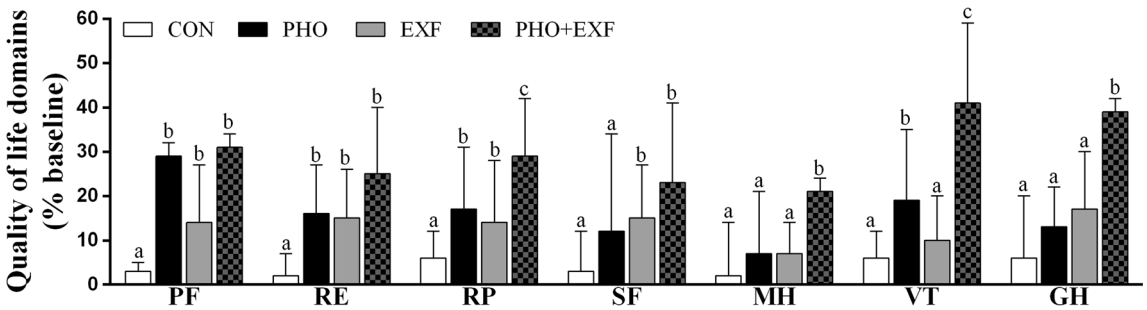

Fig. 6 Long-term effect of phototherapy and exercise training on quality of life domains. Kruskal-Wallis test (post hoc Dunn) was applied in analysis. Different letters show significant differences among groups. Similar letters show no significant differences. Data are expressed as Δ%. PF physical functioning, RE role-emotional, RP role-physical, SF social functioning, MH mental health, VT vitality, GH general health

LLLT showed to increase blood flow in a dependent manner on the increase of nitric oxide to assist healing [23]. It is important to clarify that the beneficial role of the cluster device could also be linked to the magnetic field. In a review of clinical trials, it was found that many studies have shown a beneficial role of permanent magnets on pain relief for a broad range of disorders (e.g., neuropathic, inflammatory, musculoskeletal, fibromyalgic, and rheumatic) [26].

Several authors have shown the effectiveness of LLLT in clinical FM symptoms and quality of life (e.g., pain, tender point number, fatigue, morning stiffness, and depression) [7, 27, 28]. Similar effects have been shown with LED therapy on pain, which has a minor cost and better equipment durability [4]. In our cases, a pain level reduction and pain tender points corroborate the improvement of all FIQ parameters and adverse sleeping symptoms on RDC analysis. In addition, a higher level of quality of life was associated to phototherapy. Importantly, this is the first study to evaluate the efficacy of the combined therapy of phototherapy and EXT for FM patients. Thus, a superior effect of therapeutic overlap was observed in the tender point count as well as FIQ and RDC scores. Moreover, PHO + EXT group showed higher scores of the domains of quality of life (i.e., role-physical and vitality).

Conclusions

This study provides new knowledge on the phototherapy and EXT to improve the pain in FM patients. However, a more substantial effect was noticed for the combined intervention in FM patients, in which these clinical effects have contributed to improve VAS instrument, FIQ scores, sleeping disorders, and quality of life. Consequently, the findings of this trial are predicted to provide evidence regarding the role of phototherapy and EXT as well as a combined intervention in a multimodal management program for FM patients.

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Compliance with ethical standards

Conflict of interest Ernesto Cesar Pinto Leal Junior receives research support from Multi Radiance Medical (Solon, OH, USA), a laser device manufacturer. The remaining authors declare that they have no competing interests.

Ethical approval The ethical committee of Universidade Nove de Julho approved the study protocol (number: 419.828/2013).

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