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Effects of an Aerobic Exercise Protocol Combined with Systemic Photobiomodulation on Pain, Cardiorespiratory Fitness and Functional Capacity in Women with Fibromyalgia: A Randomized, Blinded Clinical Trial

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Abstract

Importance:

Fibromyalgia (FM) is a chronic widespread musculoskeletal pain syndrome that impairs physical function, quality of life, and cardiorespiratory fitness. Although exercise is recommended for its management, combining it with intravascular laser irradiation of blood (ILIB) may enhance its therapeutic effects.

Design:

Randomized, controlled, blinded clinical trial.

Setting:

Research Laboratory, Federal University of São Paulo (UNIFESP).

Participants:

Seventy-five women with FM were randomly assigned to aerobic exercise plus active ILIB (AEAIG, n = 25), aerobic exercise plus placebo ILIB (AEPIG, n = 25), or a control group (CG, n = 25).

Intervention:

Participants in the intervention groups performed supervised aerobic exercise on a stationary bicycle combined with active or placebo ILIB twice weekly for 12 weeks.

Main Outcome Measures:

Pain intensity (Visual Analog Scale), pressure pain threshold (algometry), cardiorespiratory capacity (cardiopulmonary exercise testing [CPET]), functional capacity (6-minute walk test [6MWT]), and quality of life.

Results

Both intervention groups showed improvements in pressure pain threshold, functional capacity, muscle performance, and quality of life, with no significant between-group differences for most outcomes. Only

the active ILIB group demonstrated a significant reduction in pain intensity. No significant changes were observed in cardiorespiratory capacity.

Conclusions

Aerobic exercise improved pain-related outcomes, functional capacity and quality of life in women with FM. Active ILIB showed no consistent advantage over placebo, although it was associated with greater pain reduction. These findings support the non-pharmacological management of FM and provide a basis for future studies to optimize ILIB parameters and exercise intensity.

CLINICAL MESSAGES

- The combination of ILIB and aerobic exercise may optimize the non-pharmacological management of fibromyalgia by improving multiple clinically relevant outcomes.
- Improvements in symptom control may promote greater participation in daily activities and exercise programs.

INTRODUCTION

Fibromyalgia (FM) is a multifactorial condition characterized by chronic widespread musculoskeletal pain, fatigue, increased pain sensitivity, sleep disturbances, and cognitive impairments such as anxiety and depression [1,2]. The hallmark symptom is persistent widespread pain lasting at least three months [3,4], often accompanied by non-restorative sleep, muscle stiffness, headaches, irritable bowel syndrome, and cognitive dysfunction [5].

These symptoms negatively impact quality of life and are frequently associated with reduced mobility and decreased engagement in physical activity, leading to muscle weakness and impaired functional capacity[6]. Additionally, individuals with FM commonly present reduced cardiorespiratory fitness, including lower maximal oxygen uptake, decreased exercise tolerance, and reduced efficiency in daily activities[7]. This contributes to a cycle of inactivity, fatigue, and pain exacerbation[7,8].

Regarding the treatment of FM, it is based on both pharmacological approaches, through the use of antidepressants, muscle relaxants, analgesics, and anti-inflammatory drugs, and non-pharmacological approaches, such as physical activity [2,9]. However, concerns related to the long-term use of medications with dependency potential highlight the need for effective non-pharmacological strategies.[10,11]. Therefore, physical exercise has emerged as a central and evidence-based intervention capable of improving symptoms, functional capacity, and quality of life in individuals with FM [12,13]. Aerobic exercise, in particular, has demonstrated effectiveness in reducing pain, improving psychosocial outcomes, and decreasing fatigue [14–16]. Its benefits include enhanced cardiorespiratory capacity, improved muscle

metabolism, and positive cardiovascular and autonomic adaptations [17,18], as well as reductions in inflammation, oxidative stress, anxiety, and depression [19].

Despite these benefits, individuals with FM often exhibit low tolerance to physical exertion, experiencing increased pain and fatigue during exercise, which may limit adherence to exercise programs[8,18,20,21]. Therefore, adjunctive therapies have been investigated to enhance the effects of exercise and improve treatment adherence[22,23]. Among these, photobiomodulation (PBM) has gained attention as a non-invasive therapeutic approach. PBM involves the application of red or infrared light to biological tissues to modulate cellular processes and promote therapeutic effects [24]. At the cellular level, PBM enhances mitochondrial activity, increasing ATP production and activating signaling pathways mediated by reactive oxygen species, nitric oxide, calcium ions, and cyclic AMP [24–26]. These mechanisms promote cellular proliferation and tissue repair[24]. Clinically, PBM exhibits analgesic effects by reducing peripheral and central sensitization and activating endogenous pain inhibitory pathways [27–29]. It has also been associated with increased levels of serotonin and β-endorphins, contributing to pain relief and improved nociceptive modulation [30].

PBM can be delivered through various methods, including local application and systemic approaches such as intravascular laser irradiation of blood (ILIB) [31]. ILIB promotes systemic effects, including improved microcirculation and enhanced oxygen transport [31]. Recent studies suggest that ILIB may be effective in reducing pain and improving sleep quality in musculoskeletal conditions [32]. Additionally, transcutaneous systemic PBM applied over the radial artery has shown promising results in reducing pain and improving quality of life in patients with diabetic neuropathy [33]. However, its effects have not yet been investigated in individuals with FM.

Given the multifactorial nature of FM, combining therapeutic strategies may provide greater clinical benefits. The association between exercise and PBM has shown promising results in recent studies [22,34]. For example, Maciel et al.[35], conducted a study to evaluate the effects of PBM associated with a functional exercise program in the treatment of patients with FM and found no significant differences between groups. Despite this, there was a reduction in pain and an improvement in functional and muscle performance, as well as in depression and quality of life, in both the experimental group (active PBM, exercise, and education) and the placebo group (placebo PBM, exercise, and education).

Although exercise and PBM independently demonstrate positive outcomes, no studies have yet evaluated the combination of ILIB with structured exercise programs in FM. Considering their potential complementary mechanisms, this combined approach may enhance therapeutic outcomes. Therefore, the hypothesis of this study is that the combination of ILIB with an aerobic exercise program will be more effective in reducing pain and fatigue, and in improving cardiorespiratory fitness, functional capacity, and quality of life in women with FM. Accordingly, the aim of this study is to investigate the effects of combining an aerobic exercise protocol with systemic PBM (transcutaneous ILIB) on these outcomes in individuals with FM.

2. MATERIALS AND METHODS

2.1. Experimental Design

This study is a randomized clinical trial conducted at the Electrophysical Resources Laboratory, located in the Department of Biosciences at the Federal University of São Paulo (UNIFESP), Baixada Santista Campus. All participants were informed about the study procedures and signed an informed consent form. The trial followed the CONSORT recommendations [36]. The trial was registered at Brazilian Registry of Clinical Trials (ReBEC) RBR-64mpg85.

2.2. Volunteers

Women diagnosed with fibromyalgia (FM) participated in this study. Participants were recruited through social media advertisements and the institution's website. Sample size was calculated using G*Power software version 3.1.9.2 (Heinrich-Heine University Düsseldorf, Germany) for between-group comparisons. A significance level of $\alpha = 0.05$, power (β) = 0.80, and effect size of 0.8 were adopted. The estimated sample size was 63 participants. Considering a 20% dropout rate, 25 participants were included per group.

2.3. Experimental Groups

Participants were randomized into three groups: Aerobic Exercise + Active ILIB Group (AEAIG, n = 25), in which participants performed aerobic exercise combined with active transcutaneous ILIB; Aerobic Exercise + Placebo ILIB Group (AEPIG, n = 25), which performed aerobic exercise combined with placebo transcutaneous ILIB; and Control Group (CG, n = 25), whose participants underwent only baseline and final assessments.

2.4. Randomization

Randomization was performed using Microsoft Excel with support from RANDOM.ORG. A simple table with three columns (A, B, and C) containing random numbers was used to determine group allocation. Each participant received a random code corresponding to their assigned group. Allocation was conducted by a researcher who did not inform participants or evaluators of the assigned treatment. Both participants and outcome assessors were blinded to group allocation.

2.5. Inclusion, Non-Inclusion and Exclusion Criteria

Inclusion Criteria: Participants were required to be (1) female, (2) aged between 18 and 60 years, (3) diagnosed with FM by a physician and confirmed by a physiotherapist according to the American College of Rheumatology criteria[3,4]: Widespread Pain Index (WPI) ≥ 7 and Symptom Severity Scale (SSS) ≥ 5, or WPI 4–6 and SSS ≥ 9, with generalized pain in at least 4 of 5 body regions (excluding jaw, chest, and abdominal pain), and symptoms present for at least 3 months; (4) willing to participate in the full protocol; and (5) cognitively able to understand the procedures, assessed by the Mini-Mental State Examination.

Non-inclusion criteria

(1) uncontrolled systemic diseases (e.g., diabetes mellitus, hypertension); (2) neurological or musculoskeletal conditions interfering with assessments (e.g., paralysis, severe sensory deficits, advanced joint disease); (3) malnutrition (BMI < 18.5 kg/m²) or morbid obesity (BMI ≥ 40 kg/m²).

Exclusion criteria (intention-to-treat adjusted)

(1) withdrawal, lack of availability, or non-attendance during interventions; (2) development of conditions preventing continuation in the study.

2.6. Procedures

Participants were invited through social media. Those who expressed interest completed an online form and were scheduled for an in-person screening interview, during which eligibility criteria and clinical history were assessed. Eligible participants attended a second session for baseline clinical evaluation one week later. After group allocation, interventions began. The AEPIG group performed aerobic exercise combined with placebo ILIB, twice weekly for 12 weeks. The AEAIG group performed the same exercise protocol combined with active ILIB. The control group underwent only baseline and reassessment after 12 weeks (Fig. 1).

Figure 1. Study timeline showing allocation, intervention, and assessment timepoints

[INCLUDE FIGURE 1]

2.7. Clinical Assessment

All participants underwent clinical assessments at baseline and after the intervention period, conducted at the UNIFESP laboratory. Pain intensity was measured using the Visual Analog Scale (VAS), a unidimensional instrument with scores ranging from 0 (no pain) to 10 (worst imaginable pain) [37]. Pain was assessed at rest, during movement, and based on the highest and lowest intensity reported in the previous week.

Cardiorespiratory capacity was evaluated using the Cardiopulmonary Exercise Test (CPET), performed on a cycle ergometer with a ramp protocol to determine VO_2max [38]. The test included rest, warm-up, progressive workload increments, and recovery phases. During the test, gas exchange was continuously monitored, while heart rate was recorded using a 12-lead electrocardiogram. Blood pressure and perceived exertion, assessed using the Borg scale, were recorded every two minutes. Test termination followed standardized clinical criteria, and all procedures were supervised by a physician and trained physiotherapists in a hospital environment properly equipped for emergencies.

Functional capacity was assessed using the Six-Minute Walk Test (6MWT), considering the total distance covered along a 30-meter flat corridor with standardized verbal encouragement [39,40].

Additionally, the impact of fibromyalgia on quality of life was evaluated using the Revised Fibromyalgia Impact Questionnaire (FIQ-R), which comprises three main domains: function, overall impact, and symptoms, with higher scores indicating greater impairment [41].

The intervention protocol consisted of a 12-week aerobic exercise program, with a frequency of two sessions per week [15]. Sessions were performed on a cycle ergometer, with progressive workload adjustments every two weeks, maintaining a cadence between 50 and 60 revolutions per minute. Each session lasted approximately 30 minutes, consisting of 5 minutes of warm-up, 20 minutes of aerobic exercise, and 5 minutes of stretching. Exercise intensity was prescribed based on a percentage of the maximum heart rate obtained from the CPET, with progressive increases of approximately 5% every two weeks[15].

Additionally, a systemic PBM protocol was applied using the transcutaneous intravascular laser irradiation (ILIB) technique, employing a low-level laser device (660 nm, 80 mW, continuous mode) [42]. The application was performed over the radial artery, transcutaneously, for 30 minutes per session, twice weekly, throughout the 12-week intervention period. Both participants and therapists wore protective goggles during the procedure. In the placebo group, the protocol followed the same procedures, but without actual laser emission. During the treatment period, participant attendance was monitored using attendance sheets, with a minimum required frequency of 80% for the sessions.

2.8. Statistical Analysis

Statistical analyses were performed using GraphPad Prism 8 by a blinded researcher. Data normality and homogeneity were assessed using the Shapiro–Wilk test. A two-way ANOVA with Sidak post hoc test was used to compare group effects. Mean differences and standard deviations were calculated. Missing data were handled using multiple imputation with a random forest algorithm (intention-to-treat analysis). Statistical significance was set at $p \leq 0.05$.

3. RESULTS

In this study, 75 women were included and analyzed, with 25 participants in the CG, 25 in the AEPIG, and 25 in the AEAIG. Figure 2 presents the participant flow diagram and the anthropometric data of the volunteers in the CG, AEPIG, and AEAIG, as shown below.

[INCLUDE FIGURE 2**]**

3.1. Anthropometric characteristics

Participants in CG had a mean age of 49.6 ± 6.92 years, body mass of 76.7 ± 14.1 kg, height of 1.61 ± 0.04 m, and a body mass index (BMI) of 29.9 ± 5.04 kg/m². In AEAIG, the mean age was 48.6 ± 7.93 years, body mass was 78.8 ± 11.1 kg, height was 1.60 ± 0.07 m, and BMI was 30.7 ± 3.24 kg/m². In AEPIG, the mean age was 49.7 ± 10.2 years, body mass was 75.6 ± 13.0 kg, height was 1.59 ± 0.05 m,

and BMI was 29.7 ± 4.45 kg/m². The groups presented homogeneous baseline anthropometric characteristics, with no significant differences in age, body mass, height, and BMI ($p > 0.05$).

The intragroup analysis of Current Pain at Rest showed a significant difference only for AEAIG ($p = 0.0081$) when compared the values found in the evaluation and reevaluation, with no differences observed in for CG ($p = 0.9802$) or AEPIG ($p = 0.7337$). No intergroup differences were found ($p = 0.4092$). For Current Pain During Movement, no significant differences were observed in either the intragroup ($p = 0.1830$) or intergroup analyses ($p = 0.6269$). Regarding the Worst Pain Experienced in the Previous Week, a significant reduction was observed only in the AEAIG group ($p = 0.0389$) when compared the values found in the evaluation and reevaluation, while CG ($p = 0.1482$) and AEPIG ($p = 0.2289$) remained unchanged. No significant intergroup differences were identified ($p = 0.6234$). The Least Pain Experienced in the Previous Week showed no significant changes over time ($p = 0.8188$), nor any differences between groups ($p > 0.05$).

It was observed that only AEAIG showed a reduction in pain that approached the Minimal Clinically Important Difference (MCID) on the VAS. The variables *current pain at rest* ($\Delta = 1.65$) and *worst pain experienced in the previous week* ($\Delta = 1.72$) showed the greatest reductions after the intervention. In AEPIG and CG, the observed variations did not reach values considered clinically relevant.

Table 1
Means and standard deviations of pain intensity measures assessed by the VAS for all groups at pre- and post-intervention.

EVA	CG			AEPIG			AEAIG		
	INITIAL	**FINAL**	**Δ MCID**	**INITIAL**	**FINAL**	**Δ MCID**	**INITIAL**	**FINAL**	**Δ MCID**
Current Pain at Rest	5,24 ± 2,02	5,43 ± 1,71	-0,19	5,50 ± 2,53	5,01 ± 1,87	0,49	5,59 ± 2,08	3,94 ± 2,22*	1,65
Current Pain During Movement	5,62 ± 2,76	5,94 ± 2,58	-0,32	6,14 ± 1,85	5,74 ± 2,13	0,40	6,11 ± 2,19	4,81 ± 2,30	1,30
Worst Pain Experienced in the Previous Week	7,30 ± 2,18	8,38 ± 1,28	-1,08	8,38 ± 1,79	7,47 ± 1,60	0,91	8,14 ± 1,99	6,42 ± 2,08*	1,72
Least Pain Experienced in the Previous Week	3,68 ± 1,73	3,97 ± 1,87	-0,29	4,09 ± 2,16	3,95 ± 1,82	0,14	3,93 ± 2,04	3,08 ± 1,84	0,85

Note: CG: Control Group; AEAIG: Aerobic Exercise Group with active transcutaneous ILIB; AEPIG: Aerobic Exercise Group with placebo transcutaneous ILIB; VAS: Visual Analog Scale; Δ MCID: Intragroup Minimal Clinically Important Difference; * Statistically significant difference between time points pre- and post-intervention ($p \leq 0.05$).

3.3. Pressure pain threshold

The values of pressure pain threshold are presented in Table 2. No significant intragroup or intergroup differences were observed for the right trapezius, left gastrocnemius, or right and left biceps femoris ($p > 0.05$). For the left trapezius and left gastrocnemius, a significant intragroup increase was observed for both AEPIG ($p = 0.0118$ and $p = 0.0143$, respectively) and AEAIG ($p = 0.0258$ and $p = 0.0440$, respectively), while no changes were found for CG ($p > 0.05$). No significant intergroup differences were detected ($p > 0.05$). Regarding the right biceps femoris, no significant intragroup changes were observed in the CG ($p = 0.9985$) or AEPIG ($p = 0.9979$), whereas the AEAIG group showed a significant increase ($p = 0.0028$). Intergroup analysis at the final time point revealed significant differences between CG and AEPIG ($p = 0.0469$), as well as between CG and AEAIG ($p = 0.0021$). For the left quadriceps, a significant intragroup increase was observed only in the AEAIG ($p = 0.0380$), with no changes in CG ($p = 0.7272$) or AEPIG ($p = 0.7748$). No significant intergroup differences were identified ($p > 0.05$).

Table 2
Means and standard deviations of pain intensity measures assessed by pressure algometry for all groups at baseline and final time points.

ALGOMETER	CG		AEPIG		AEAIG	
	INITIAL	FINAL	INITIAL	FINAL	INITIAL	FINAL
Trapezius R	1,78 ± 0,93	1,21 ± 0,46	1,47 ± 0,59	1,61 ± 0,47	1,66 ± 0,79	1,71 ± 0,59
Trapezius L	1,71 ± 0,83	1,13 ± 0,48	1,11 ± 0,74	1,93 ± 0,49*	1,04 ± 0,94	1,99 ± 0,75*
Biceps R	1,08 ± 0,67	0,98 ± 0,38¹	1,07 ± 0,41	1,36 ± 0,40¹	1,3 ± 0,60	1,89 ± 0,58¹
Biceps L	1,14 ± 0,69	0,97 ± 0,39	1,08 ± 0,59	1,16 ± 0,50	1,51 ± 0,88	1,30 ± 0,45
Quadriceps R	1,91 ± 0,94	1,76 ± 0,46	1,99 ± 0,94	2,02 ± 0,53	2,58 ± 1,28	2,20 ± 0,81
Quadriceps L	2,17 ± 0,86	1,97 ± 0,68	2,00 ± 0,81	1,97 ± 0,59	2,07 ± 0,67	2,55 ± 1,10*
Gastrocnemius R	2,27 ± 1,16	2,20 ± 0,61	2,78 ± 1,84	2,60 ± 0,81	2,18 ± 0,96	2,51 ± 0,99
Gastrocnemius L	2,20 ± 1,49	2,16 ± 0,71	2,16 ± 1,32	2,88 ± 0,84*	2,14 ± 0,81	2,53 ± 1,18*

Note: CG: Control Group; AEAIG: Aerobic Exercise Group with active transcutaneous ILIB; AEAIG: Aerobic Exercise Group with placebo transcutaneous ILIB; L: Left; R: Right; * *Statistically significant difference between time points pre- and post-intervention (p ≤ 0.05);* ¹ *Statistically significant intergroup difference at the final time point (p ≤ 0.05).*

3.4. Cardiorespiratory and functional capacity

No statistically significant intragroup or intergroup differences were found in the CPET assessment (p > 0,05), as illustrated in Fig. 3a.

In the 6MWT assessment, a significant increase was observed in the distance covered by participants in both AEPIG (p = 0.03) and AEAIG (p = 0.01). Furthermore, intergroup differences were identified at the final time point, with CG showing a significantly shorter distance compared to both AEPIG (p = 0.0002) and AEAIG (p = 0.0017), as illustrated in Fig. 3b.

Figure 3. a. Oxygen consumption (VO_2) at baseline and final time points of the studied groups; **b.** Performance in the 6-Minute Walk Test (6MWT)

[INCLUDE FIGURE 3]

Note

CG: Control Group; AEAIG: Aerobic Exercise Group with active transcutaneous ILIB; AEPIG: Aerobic Exercise Group with placebo transcutaneous ILIB; VO_2 (mL/min/kg): Oxygen consumption per minute per kilogram of body weight; * *Statistically significant difference ($p \leq 0.05$)*.

3.6. Impact of FM on Quality of Life

For the domain function, AEPIG and AEAIG showed significant intragroup differences ($p < 0.0001$ for both), whereas CG showed no change significant ($p = 0.3040$), with no intergroup differences ($p = 0.0809$). For overall impact, intragroup improvement was observed in AEPIG ($p = 0.0001$) and AEAIG ($p = 0.0030$), with no change in the CG ($p = 0.9995$) and no intergroup differences ($p = 0.1177$). In the symptoms domain, intragroup differences was observed in AEPIG ($p = 0.0248$) and AEAIG ($p = 0.0064$), while the CG remained unchanged ($p = 0.8979$), with no intergroup differences ($p = 0.2642$). In the final score, AEPIG ($p = 0.0004$) and AEAIG ($p < 0.0001$) showed significant intragroup difference, with no change for CG ($p = 0.0763$) and no intergroup differences ($p > 0.05$), as shown in Table 3.

Table 3
Means and standard deviations of FIQ-R-related measures for all groups at the initial and final time points.

FIQ-R	CG		AEPIG		AEAIG	
	INITIAL	FINAL	INITIAL	FINAL	INITIAL	FINAL
Function	17,7 ± 5,4	15,53 ± 5,43	20,1 ± 4,55	13,4 ± 4,65*	16,8 ± 5,88	11,5 ± 5,03*
Overall impact	14,0 ± 5,55	14,12 ± 4,83	15,8 ± 3,91	10,64 ± 5,57*	13,6 ± 5,05	9,64 ± 5,24*
Symptoms	36,02 ± 5.79	49,3 ± 44,47	40,6 ± 12,56	31,17 ± 7,86*	37,1 ± 6,12	29,7 ± 10,12*
Final Score	67,7 ± 14,04	63,7 ± 19,54	74,7 ± 10,52	55,07 ± 15,8*	67,7 ± 13,9	49,4 ± 17,25*

Note: CG: Control Group; AEAIG: Aerobic Exercise and Active Transcutaneous ILIB Group; AEPIG: Aerobic Exercise and Placebo Transcutaneous ILIB Group; * Statistically significant difference over time (initial vs. final).

4. DISCUSSION

The present study investigated the effects of the association between aerobic exercise and transcutaneous ILIB in women with FM. The main findings demonstrated that aerobic exercise, either isolated or associated with ILIB, was capable of reducing pressure pain threshold and fatigue, in addition to improving the quality of life of the participants. Pain intensity, assessed using the VAS, showed significant intragroup differences only in the AEAIG. On the other hand, no significant differences in cardiorespiratory capacity were observed in either group. Overall, the AEAIG did not demonstrate superiority compared to the AEPIG, with no significant differences observed between groups.

It is well known in the literature that physical exercise activates central pain modulation mechanisms, based on the increasing release of endorphins, serotonin, and improvement of descending inhibitory pain control, frequently compromised in individuals with FM [43]. Cortés et al., [44] in a systematic review with meta-analysis, report that physical exercise promotes pain reduction in individuals with FM, with better results observed in protocols lasting at least 90 minutes per week. The aerobic exercise protocol used in the present study was performed twice a week, lasting 30 minutes per session which is aligned with the recommended guidelines for this population [45]. In the present study, difference in the variables evaluated by VAS was observed only in the group that performed exercise and received active ILIB application (reduction in pain at rest and worst pain reported in the previous week), in addition to presenting the highest values of minimal clinically important change. PBM exerts analgesic effects, contributing to pain reduction and improvement of clinical outcomes [46]. When associated with physical exercise, PBM can improve the analgesic effects, resulting in optimized treatment. In the clinical trial by Da Silva et al., [22], they demonstrated that physical exercise associated with PBM is effective in reducing pain in individuals with FM, reinforcing the potential benefit of the combined approach. In spite of the lack of no significant intergroup differences, the reductions in pain intensity observed in the exercise and active ILIB group, including MCID, are aligned with the literature. Conversely, the pressure pain threshold results demonstrated a significant improvement in the left gastrocnemius and left trapezius muscles, observed in the AEPIG. These findings suggest an improvement in nociceptive modulation and possible reduction of central sensitization after the performance of the physical exercise program in the exercised individuals with FM [47,48]. Additionally, AEAIG also demonstrated statistically significant gains related to the pressure pain threshold in the left trapezius, quadriceps, and gastrocnemius muscles. Navarro-Ledesma et al., [49] showed that PBM was capable of significantly increasing the pressure pain threshold assessed by algometry, reinforcing the findings of the present study, since they also observed an increased pain threshold after interventions with exercise and PBM; however, without demonstrating superiority of PBM compared to placebo, reinforcing the predominant role of exercise in this outcome.

Similarly, factors related to effort tolerance can also influence variables associated with cardiorespiratory capacity. In this study, VO_2max evaluation has not demonstrated significant improvements at the end of the intervention in both evaluated groups. Individuals with FM frequently present reduced aerobic capacity when compared to healthy individuals, a condition generally associated with physical deconditioning related to chronic pain, which in general contribute to sedentarism and low tolerance to physical exercise [8]. The results of the present work did not corroborate to those of Andrade et al.,[50] who observed significant increase in VO_2max after an aquatic exercise program lasting 16 weeks in women with FM. This difference may be related to differences in the type and duration of intervention, since more prolonged protocols tend to promote more evident cardiorespiratory adaptations. Additionally, aquatic exercise is characterized by the absence of joint impact, which may favor greater effort tolerance and better training adherence, potentiating gains in aerobic capacity. Furthermore, PBM is capable of stimulating mitochondrial metabolism and increasing energy availability for muscle cells, potentially contributing to improved performance and VO_2max.

Miranda et al.[38] demonstrated that the application of PBM before exercise was capable of significantly increasing the time to exhaustion and pulmonary ventilation during progressive cardiopulmonary exercise tests, in addition to reducing dyspnea scores. However, it should be emphasized that the positive effects observed in this study occurred in healthy individuals. The results demonstrated that the addition of ILIB to aerobic exercise did not provide any additional effect on VO_2max compared with aerobic exercise combined with placebo, with no significant intergroup differences observed. Furthermore, the absence of significant improvements in either group suggests that the interventions were not sufficient to promote measurable cardiorespiratory adaptations. Therefore, the potential bioenergetic effects attributed to ILIB do not appear to have impacted the participants' cardiorespiratory capacity under the conditions evaluated in this study. In addition, the duration of the intervention, the parameters applied, and the clinical complexity of FM, characterized by widespread chronic pain, fatigue, and physical deconditioning, may have limited the occurrence of physiological adaptations detectable by cardiopulmonary exercise testing.

Complementarily, performance in the 6MWT provides a relevant functional measure of exercise capacity, being a reliable indicator of functional capacity [39,51]. In the present study, AEPIG demonstrated a significant increase in distance covered. Similar results were observed in the clinical trial developed by Mannerkorpi et al., [52] who evaluated women with FM subjected to exercise programs, with significant improvement identified in 6MWT performance after intervention, reinforcing the role of exercise in functional capacity of this population. Additionally, the exercise and active ILIB group also showed significant improvement in 6MWT. These findings are in line with the randomized clinical trial performed by da Silva et al.,[22], who demonstrated that the association between PBM and physical exercise promotes improvement in pain and functional performance in individuals with FM. However, no extra effect was observed in the exercised irradiated volunteers during functional capacity evaluation. These results corroborate and were discussed by Vassão et al., [34] who also did not observe significant differences between groups in 6MWT evaluation. The hypothesis that the dosage used may have exceeded the ideal stimulus for these patients or that the isolated efficacy of interventions made it difficult to detect additional benefits of combined therapy. Thus, the clinical complexity of FM and the efficacy of exercise adaptations reinforce the need for new protocols to verify the additive effect of PBM.

Similarly, significant improvements were also identified in the impact of FM on participants' quality of life. Analysis of FIQ-R domains demonstrated significant reduction in all scores of the AEPIG, indicating global improvement in functional, physical, and emotional aspects related to the disease. These findings suggest that aerobic exercise contributed to reduce the disease impact on daily activities and participants' health status perception. These positive results are due to the multifactorial action of physical exercise, which promotes not only pain reduction but also improved functional capacity and modulation of psychosocial aspects, such as mood and well-being perception. Considering that FM has a complex nature and involves multiple domains, interventions that act broadly tend to generate more significant impacts on quality of life. This corroborates the studies by Rodríguez-Mansilla et al., [53] who observed improvement in well-being, pain reduction, and increased quality of life after an exercise

program in individuals with FM. Additionally, although the AEAIG also obtained statistically significant differences in all FIQ-R domains, no statistical differences were observed between groups, showing no additional effect of ILIB compared to placebo. Similarly, Maciel et al., [54] evaluated the effect of PBM associated with a functional exercise program in individuals with FM and verified that both groups had positive effects without extra effects from PBM. The results of both groups indicate that isolated exercise was capable of acting effectively to improve quality of life.

The present study has some limitations that should be considered in interpreting results. The duration of the intervention period may have influenced the magnitude of observed adaptations, since more prolonged interventions can potentiate clinical and functional effects in individuals with FM. Considering that the present study assessed the effects of aerobic exercise combined with ILIB only at baseline and immediately after the 12-week intervention, future studies should investigate whether these effects are maintained during longer follow-up periods. Additionally, the parameters used for ILIB application were previously defined by the equipment manufacturer, and there is still no consensus in the literature regarding ideal parameters of this therapeutic modality. Another relevant aspect refers to the clinical characteristics of FM, especially the presence of widespread pain, which can influence participants' adherence and tolerance to regular physical exercise practice. Finally, the absence of follow-up after intervention completion limits the evaluation of long-term maintenance of observed effects.

5. CONCLUSION

In conclusion, this randomized clinical trial demonstrated that aerobic exercise was effective in improving pain, functional capacity, fatigue, and quality of life in women with FM. Although transcutaneous ILIB showed some promising effects, especially in pain-related outcomes, aerobic exercise appears to have been the primary therapeutic factor. The absence of improvements in maximal cardiorespiratory fitness, despite gains in functional capacity, highlights the complex and multifaceted nature of therapeutic adaptation in this population and suggests that patient-centered outcomes may be more relevant than traditional exercise physiology endpoints. Further studies are needed to optimize PBM parameters and investigate the benefits of combined interventions.

Declarations

Author Contribution

Thatiane Izabele Ribeiro Santos (Conceptualization [Lead], Formal analysis [Lead], Investigation [Lead], Writing—original draft [Lead]), Cristiano Carvalho (Conceptualization [Lead], Writing—review & editing [Supporting]), Cassia Maria Campos Melo (Methodology [Supporting], Investigation [Supporting]), Ana Caroline da Silva Fernandes (Data curation [Lead], Writing—original draft [Supporting], Writing—review & editing [Lead]), Helena Mayumi Akashi (Data curation [Lead], Writing—original draft [Supporting]), Alice Torres Pontes (Writing—review & editing [Supporting], Visualization [Supporting]), Júlia Ghraziely Justino de Oliveira (Methodology [Supporting], Investigation [Supporting]), Catharina Marabiza Pinheiro

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Data Availability

All data supporting the conclusions of this study are available within the article and its Supplementary Information.

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Figures

Figure 1. Study timeline showing allocation, intervention, and assessment timepoints

TRIAL PERIOD							
	Enrollment	Randomization	Baseline Assessment	Post-randomization			Close-out
TIMEPOINT	$-t_1$	0		week 4	week 8	week 12	
Enrollment:							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
INTERVENTION							
Aerobic Exercise + Active ILIB Group (AEAIG)				X	X	X	
Aerobic Exercise + Placebo ILIB Group (AEPIG)				X	X	X	
Control Group (CG)				X	X	X	
ASSESSMENTS							
Visual Analog Scale (VAS)			X				X
Algometer			X				X
Cardiopulmonary exercise test (CPET)			X				X
6-Minute Walk Test (6MWT)			X				X
Revised Fibromyalgia Impact Questionnaire (FIQ-R)			X				X

Figure 1

Study timeline showing allocation, intervention, and assessment timepoints

Figure 2. Participant flow diagram

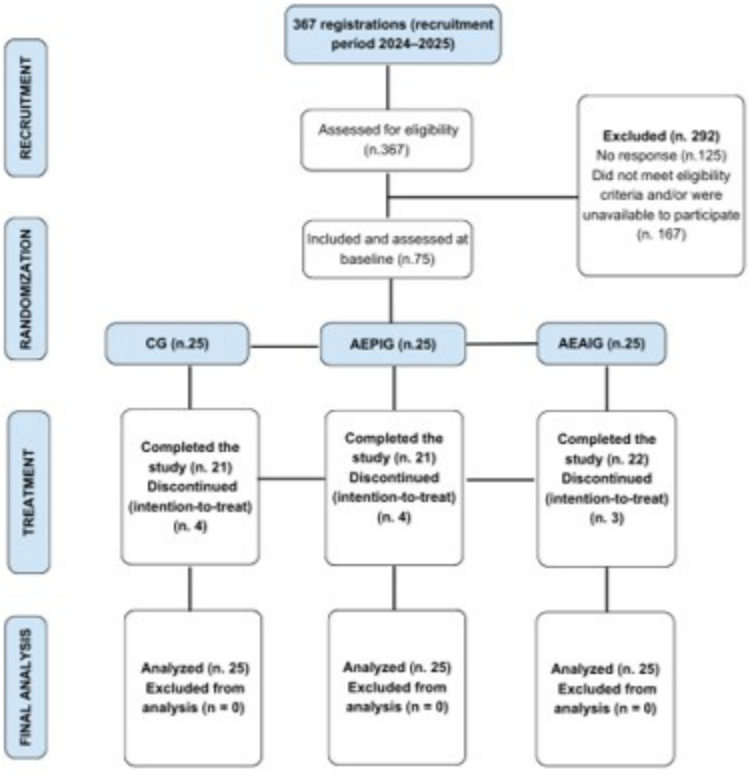


Figure 2

Participant flow diagram

Figure 3. a. Oxygen consumption (VO_2) at baseline and final time points of the studied groups; **b.** Performance in the 6-Minute Walk Test (6MWT)

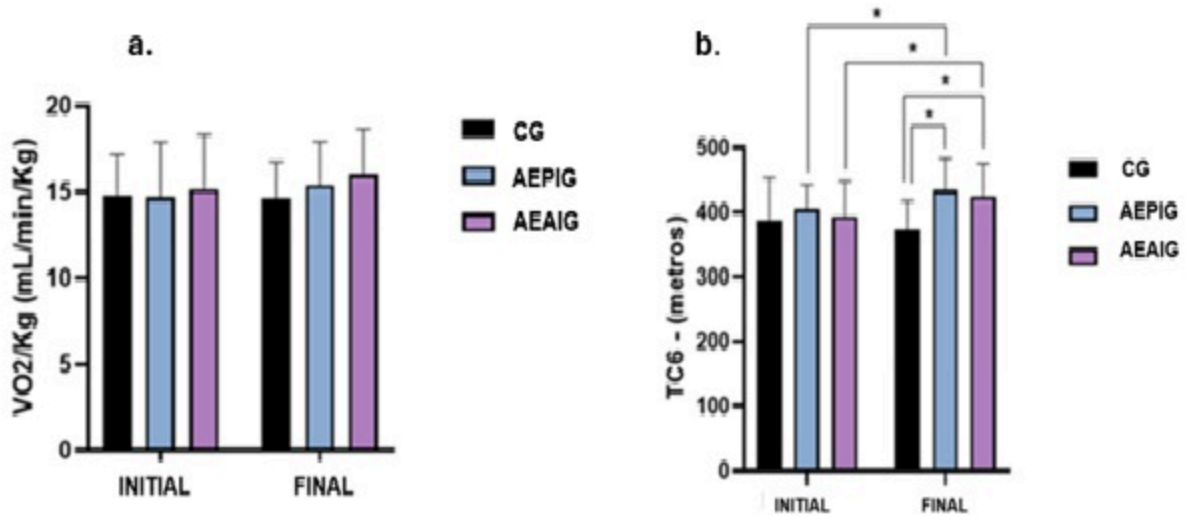


Figure 3

a. Oxygen consumption (VO_2) at baseline and final time points of the studied groups; **b.**Performance in the 6-Minute Walk Test (6MWT)

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