Short- and Long-term Effects of Photobiomodulation on Pain, Functionality, Tissue Quality, Central Sensitisation and Psychological Factors in a Population Suffering From Fibromyalgia: Protocol for a Triple-blinded Randomized Clinical Trial.

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Study protocol

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Abstract

Background: The development of an integral and global treatment to improve the quality of life in those with fibromyalgia syndrome (FMS) is challenging.

Methods: This study is a randomized, placebo-controlled clinical trial. Participants will be recruited in a private care practice and randomized to receive either a whole body Photobiomodulation (PBM) therapy program or placebo. Primary outcomes will be pain (Numeric Pain Rating Scale; Widespread Pain Index; Symptom Severity Score), functionality (Fibromyalgia Impact Questionnaire; The Leisure Time Physical Activity Instrument), quality of soft tissue (elastography) and central sensitisation (pain pressure threshold and the Autonomic Symptom Profile). Secondary outcomes will be psychological factors (Pain Catastrophising scale, Tampa Scale, Self-Efficacy questionnaire). Assessments will be at baseline (T1), after session 6 (T2), after treatment (T3) and 2 weeks (T4), 3 (T5) and 6 (T6) month follow-up.

Discussion: PBM therapy has been shown to reduce pain and inflammation and to increase the rate of tissue repair for a wide range of conditions, but its potential use as a whole body treatment in FM is yet to be explored. This trial will investigate whether whole body PBM therapy is effective at reducing pain intensity, improving functionality, quality of soft tissue, central sensitisation symptoms and psychological measurements. Furthermore, 3 and 6 months follow up will investigate long-term efficacy of this treatment.

Trial registration: NCT04248972. Registered on January 29, 2020, <https://clinicaltrials.gov/ct2/show/NCT04248972?term=navarro-ledesma+santiago&draw=2&rank=2>.

Background

Fibromyalgia syndrome (FMS) is a chronic and multicomponent illness with unknown etiology and is considered the most frequent cause of diffuse chronic musculoskeletal pain[1]. Following the American College of Rheumatology (ACR), different criteria have been included in FMS diagnosis, such as digital pain pressure sensitivity at a pressure of 4 kg and widespread pain, criteria which cannot be explained by the presence of degenerative or inflammatory disorders, cognitive behavior disorders, restless sleep, fatigue, and somatic symptoms [2, 26]. This syndrome can occur in all ages, but it is more common in middle-aged adults[3]. In the general population, the range is from 0.5–5%, and up to 15.7% in a clinical setting. In Spain, the estimated prevalence is 4.2% in women and 0.2% in men[1].

Despite some physical therapy interventions, such as exercise and cognitive behavior therapy showing some therapeutic benefit[2–4], FMS is a complex syndrome and there is little evidence to confirm if the condition is fully improved in all aspects using these treatment programs. Thus a multifactorial and definitive treatment is currently lacking[2, 4, 5].

Photobiomodulation (PBM) therapy, formerly known as Low-level laser therapy (LLLT), is an emerging, non invasive and promising therapy for those suffering from FMS, since it has shown positive impact on

relieving musculoskeletal and neuropathic pain, with consequent improvement on quality of life[5]. Current research has established effective wave lengths of light used for PBM to range from 600 to 1070 nm, with a fluence (energy density) range of between 1 and 20 J/cm². Effective tissue penetration is maximised in this range, as the principal tissue chromophores (haemoglobin and melanin) have high absorption bands at wave lengths shorter than 600 nm. Wavelengths in the range 600–700 nm are used to treat superficial tissue, and longer wave lengths in the range 780–950 nm, which penetrate further, are used to treat deeper-seated tissues[6, 7].

People suffering from FMS usually present with tender points in a number of anatomical areas, in fact 95% of people with chronic pain disorders have been shown to present with myofascial pain[8]. Tender or trigger points are the result of a nonspecific response of the central nervous system in its interaction with the autonomic nervous system[9].

Ultrasound elastography (USE) imaging can provide an objective and reproducible measure of a change in the status of myofascial trigger points as determined by physical examination, since palpably stiff nodules vibrate with lower amplitude than healthy tissue when using ultrasound[8]. The USE was first described in the 1990s, and recently developed in order to assess quantitatively tissue stiffness; thus there has been an increase in the use of USE to measure changes in elasticity of soft tissues in the study of physiological processes and pathology[10, 11].

In addition to pain, presence of tender points and central sensitisation, other postural, balance and functional symptoms have also been presented in those with FMS[4, 12–14] affecting psychological health, ability to enjoy leisure activities and consequently quality of life[12, 15, 16]. It is therefore important to also include outcome measures of these symptoms in investigative research.

We hypothesise that a whole-body application of PBM will improve pain, functionality, quality of soft tissue, central sensitisation and psychological symptoms in patients suffering with FMS.

To our knowledge, this is the first study to use whole body PBM in FMS patients.

Methods

Design

This is a triple-blinded, randomized, placebo-controlled clinical trial with blinding of participants, therapists and statistician to active or placebo whole body PBM.

Setting

Participants will be recruited in a private care practice in Malaga, Spain. Potential referrals will be informed of the trial through formal meetings and trial information sheets. This study is reported in line with the Standard Protocol Items; Recommendations for Interventional Trials (SPIRIT) Statement[17].

Patients involvement

Patients will be involved in the design and conduct of this research. During the feasibility stage, priority of the research question, choice of outcome measures, and methods of recruitment will be informed by discussions with patients through a focus group session. Once the trial has been published, participants will be informed of the results through a new session and they could ask for the details of the results.

Participants

Participants will be screened by a physiotherapist to determine whether they meet the following inclusion and exclusion criteria:

Inclusion criteria

i) Aged between 34 and 64 years

ii) FMS diagnosis according to the ACR classification criteria (modified 2010/2011)[18]. To diagnose fibromyalgia in adults, it is necessary for all of the following criteria to be met: (1) Present generalised pain, i.e., in at least four of five regions, (2) Present symptoms for at least 3 months at similar levels, (3) Symptom severity scale (SSS) score ≥ 5 and Widespread pain index (WPI) ≥ 7 ; or SSS score ≥ 9 and WPI between 4 and 6, and (4) A diagnosis of fibromyalgia does not exclude the presence of other illnesses and is valid irrespective of other diagnoses.

Exclusion criteria

Presenting any inflammatory, neurological, or orthopaedic disease which can alter balance, hearing, and vision, or cognitive impairment, which might impact on ability to answer questions.

Participants will be randomized to receive either a whole body PBM therapy or placebo.

Patients will be required to not receive or participate in any other FMS study or treatment during the study period. Any change in medication type or dosage during the study period will be recorded.

The interventions are described following Template for Intervention Description and Replication (TIDieR) Checklist recommendations[19]

PBM therapy program

Participants randomized to this treatment will receive a whole body PBM treatment using a NovoTHOR® whole body light bed (Fig. 1.). For each treatment session, participants will lie supine in the treatment bed for 20 minutes, with no or minimal attire (underwear). Treatment sessions will be three times weekly for a period of 4 weeks, totalling 12 treatment sessions. The parameters of the equipment are shown in Table 1.

#Fig. 1: NovoTHOR bed

Table 1
NovoTHOR parameters

NovoTHOR XL Parameters		Unit
Wavelengths of red and near-infrared (NIR) LEDs 50:50 ratio	660	nm
	850	nm
Number of LEDs	2,880	
Power emitted per LED	0.336	W
Beam area per LED (at the lens/skin contact surface)	12.0	cm ²
Total Power emitted	967	W
Total Area of NovoTHOR emitting surfaces	34,544	cm ²
Treatment Time	1200	s
Continuous Wave (CW) (not pulsed)	CW	
Irradiance	0.028	W/cm ²
Fluence	25.2	J/cm ²

Placebo feature

The placebo feature of the whole body PBM bed provides controls that select active or placebo (sham) treatments in a way undetectable by participant, operator or observers, such that no-one is aware whether the participant is receiving an active or placebo treatment. There is a switch box (see Fig. 2) that randomises participants to active or placebo; no other randomisation is necessary.

#Fig. 2: NovoTHOR randomising switch box

Special goggles that block the PBM light are worn by the participant, operator and observers. These emit LED light inside (behind the lenses, so that the wearer sees some red light) to make it harder for participants, operator or observers to detect if the PBM bed is active or placebo. The goggles are designed to accommodate spectacles.

Heating elements also come on in the NovoTHOR bed when the PBM bed is in placebo mode, so that participants feel like they are in the real treatment.

PBM is safe, and easy to administer, is non invasive and has no known side effects, with few reported contraindications[20].

For each treatment session, participants will lie supine in the treatment bed for 20 minutes, with no or minimal attire (underwear). Treatment sessions will be three times weekly for a period of 4 weeks,

totalling 12 treatment sessions.

Data collection

Assessment of primary and secondary outcome measures will be at baseline, after treatment 6, immediately following the last treatment (4 weeks), and then 2 weeks and at 3 monthly follow up intervals to 6 months after completion of treatment. A flow diagram illustrates these assessment times (Fig. 3)

#Fig. 3: Flow diagram illustrating the assessments times.

Outcome measures

The primary outcome measures:

1. 1.The Numeric Pain Rating Scale (NPRS), where 0 indicates “no pain,” and 10 indicates “worst possible pain.” At each measurement point of the study, patients of both groups will be asked to rate the average intensity of their pain over the past 7days. This procedure has demonstrated a high degree of validity and reliability[21].
2. 2. The Leisure Time Physical Activity Instrument (LTPAI), used to measure the physical activity. This has four components, each with three levels of activity: light, medium, and vigorous. Scores indicate the number of hours which these activity levels had been carried out each week in the last four weeks summing as the total number of hours of physical activity[22]. This tool has shown satisfactory test–retest reliability for the total score, i.e., ICC = 0.86 (CI 0.79–0.93), and for the PAHWI (ICC 0.91, CI 0.82–9.96)[22].
3. 3. Widespread Pain Index (WPI), a questionnaire which shows appropriate distribution and a sufficient number of body quadrants and axial skeleton pain representation. It is part of the FMS diagnosis[23].
4. 4. Symptom Severity Score (SSS), a questionnaire which is part of the FMS diagnosis[23].
5. 5. The revised Fibromyalgia Impact Questionnaire (FIQR), a self-administered questionnaire comprising 21 individual questions, with a rating scale of 0–10. The questions compose three different domains: function, overall impact and symptoms score (range 0–30, 0–20 and 0–50, respectively) [24, 25]. The FIQR total score ranges from 0 to 100, with a higher score indicating a greater impact of the condition on the person’s life.
6. 6. Pain pressure threshold. 12 tender points will be assessed according to the ACR criteria using a standard pressure algometer (FPK 20; Wagner Instruments, Greenwich, CT, USA.): occiput at the suboccipital muscle insertions, low cervical at the anterior aspects of the intertransverse spaces at C5-C7, trapezius at the midpoint of the upper border, supraspinatus at origins, above the scapula spine near the medial border, paraspinous 3 cm lateral to the midline at the level of the mid-scapula, second rib at the second costochondral junctions, just lateral to the junctions on the upper surfaces, lateral pectoral at the level of the fourth rib at the anterior axillary line, lateral epicondyle 2 cm distal to the epicondyles, medial epicondyle at the epicondyles, gluteal at the upper outer quadrants of buttocks in anterior fold of muscle, greater trochanter just posterior to the trochanteric prominence,

and knees at the medial fat pad proximal to the joint line, forearm at the distal dorsal third of the forearm, thumbnail, and midfoot at the midpoint of the dorsal third metatarsal[26]. The mean of 2 measurements at each tender point will be used for the analysis. The total count of positive tender points will be recorded for each participant[26].

7. 7. The Autonomic Symptom Profile (ASP), is a validated self-report questionnaire that comprehensively assesses autonomic symptoms across 11 subscales and yields a composite autonomic symptom score.
8. 8. Quantified USE in tender points. Changes in the status of myofascial trigger-points can be demonstrated with an objective and reproducible USE measure[8].

Secondary outcome measures:

1. 9. The Pain Catastrophising Scale, a validated questionnaire to assess the mechanism by which catastrophising impacts on pain experience[27].
2. 10. The Spanish version of the Tampa Scale of Kinesophobia, a valid and reliable measure of fear of movement[28].
3. 11. The self efficacy questionnaire, which assesses personal confidence to carry out an activity with the aim of successfully achieving a desired outcome[29].

Recruitment procedures

Participants will be recruited from a private clinic and rehabilitation service of Malaga (Spain). In addition, advertisements on social media will be placed to increase the potential number of participants in the study. The physiotherapist in contact with the participants for recruitment will provide information about the study, including details of eligibility criteria. Following informed consent, participants will be randomised to an active or placebo whole body treatment.

To improve the adherence to the treatment the physiotherapist administering the treatment will be in regular contact with the participants in reminding of the time schedule and follow-up sessions to them.

Statistical Analysis

SPSS® Statistics version 21.0 (IBM, Chicago, IL, USA) will be used for all analyses. The Shapiro-Wilk test will be used to verify data distribution normality. To study intra-group mean differences for all the outcomes between the six assessment times (baseline (T1), after session 6 (T2), immediate post-intervention (T3), 2 weeks after final treatment (T4), and 3 (T5) and 6 (T6) month' follow-up), repeated measures analysis of variance ANOVA will be used. To compare the two groups (PBM intervention and placebo groups) at baseline and follow-ups regarding clinical characteristics, a six-way repeated measures ANOVA will be conducted, with six levels corresponding to every time of assessment (T1, T2, T3, T4, T5 and T6), and the two intervention groups as independent factors. A p-values < 0.05 will be considered to be statistically significant.

Between- and within-group effect sizes for all quantitative variables will be measured with the Cohen d coefficient. An effect size greater than 0.8 will be considered large, around 0.5 moderate, and less than 0.2 small[30].

Sample Size Calculation

Sample size for this trial is based on an expected mean difference between groups of 2 points of the NPRS, which is the minimum clinically important difference[31]. The mean assumed for the calculation will be 5.95, with a standard deviation (SD) of 2.06 points, based on results of other randomized clinical trials[32]. To detect this difference between the intervention and placebo groups, with a value of $\alpha = 0.05$ and a statistical power of 90%, a minimum of 22 patients per group is needed.

Data management

Data from the study will be only accessible to the research team and will be stored on password-protected computers at the University of Granada. Paper-form data will be stored in locked cabinets located at the Department of Physiotherapy of that same university. In order to preserve data confidentiality study participants will be assigned an identification number which will be kept for the duration of the study. A list of participant identification numbers will be created and separated from the de-identified data.

Statistical analyses will be performed keeping participant anonymity by using patient identification numbers and the statistician will be blinded to group allocation. Confidentiality will also be preserved when disseminating results by using group data.

Discussion

Trial Status

This trial is recruiting participants from Jan.30, 2021, and will be completed on Dec. 30, 2021. The protocol version number is PBMFM-3 with date Jan. 22, 2020.

The aim of this study is to investigate the impact of whole body PBM on pain perception, functionality, quality of soft tissue, central sensitisation and psychological factors in patients suffering with FMS.

We hypothesise that the use of a whole body PBM application will improve the FMS condition, in terms of pain, functionality, quality of soft tissue, central sensitisation and consequently psychological factors and quality of life.

Moreover, we will investigate the longer-term impact of the PBM program will further investigate with follow up of outcome measures after treatment 6, immediately following the last treatment (4 weeks), and then 2 weeks and at 3 monthly follow up intervals to 6 months after completion of treatment.

To our knowledge, this is the first study developed in participants with FMS using a whole body PBM approach. PBM acts on the mitochondria, specifically photoreceptors within the mitochondrial respiratory chain. Those suffering from FMS may present compromised mitochondrial respiration and decreased ATP synthesis. Therefore, they may show a lack of energy in response to any physical activity[8, 33, 34]. This allows an increase in sensitisation of the whole body over time, leading to chronicity of pain and tenderness of soft tissue in those with FMS[5, 8, 9]. Similarly, chronic pain is associated with fatigue as well as having psychological impact[34].

Against this background, a PBM treatment is proposed to stimulate an upregulation of mitochondrial activity through acting on the mitochondrial respiratory chain, which consequently increases ATP production into muscle cells and decreases oxidative stress and reactive oxygen species production. Furthermore, a single irradiation with PBM has been demonstrated to increase cytochrome c-oxidase activity in intact skeletal muscle tissue 24 hours after irradiation. Importantly, immune cells (mast cells in particular) appear to be strongly affected by PBM, and there is considered to be a crucial role of the movement of leukocytes in inflammation. PBM causes an increase not only in ATP but also in NADH, protein, and RNA, as well as a reciprocal augmentation in oxygen consumption.[35]

Mechanistic actions of PBM at the cellular level, with resultant changes in downstream signalling pathways may lead to improvements in pain, function, quality of soft tissue, central/peripheral sensitisation and consequently psychological impact in FMS patients.

The results of this study will elucidate the therapeutic benefits of a whole body PBM approach as a novel treatment for patients with FMS, for which there is little evidence of positive impact of other treatments.

Anticipation dates of trial commencement and Completion

Commencement January 2020. Completion December 2021.

Abbreviations

American College of Rheumatology (ACR)

Fibromyalgia Syndrome (FMS)

Photobiomodulation (PBM)

Standard Deviation (SD)

Symptom severity scale (SSS)

Template for Intervention Description and Replication (TIDieR)

The Autonomic Symptom Profile (ASP)

The Leisure Time Physical Activity Instrument (LTPAI)

The Numeric Pain Rating Scale (NPRS)

The revised Fibromyalgia Impact Questionnaire (FIQR)

Ultrasound elastography (USE)

Widespread pain index (WPI)

Declarations

The trial has been registered at [Clinicaltrials.gov](https://clinicaltrials.gov) with the identifier: NCT04248972

The results of the study will be disseminated at several research conferences and as published articles in peer-reviewed journals. The full protocol and participant-level dataset will be available when this study will be finished.

Ethics approval and consent to participate: This study protocol has received ethical approval by Ethics Committee of Human Research of the University of Granada, Spain (1044/CEIH/2020). All the participants will accept and sign an informed consent before beginning the study.

Availability of data and materials: Protocol modifications will be notified to relevant parties. All members of the Research Team will have access to the final trial dataset. They will not have any responsibility for the coordinating centre, Steering Committee, Endpoint Adjudication Committee, Data Management Team, and other individuals or groups overseeing the trial.

Competing interests: James D. Carroll is the owner of THOR Photomedicine, a company which sells LLLT devices. Patricia Burton affiliation is THOR Photomedicine.

Funding: This research has been funded by THOR Photomedicine by providing the equipment needed. The role of the funding body in the research will be the study conception and design as well as revision of final manuscript.

Authors' contributions : All authors contributed to the study conception and design. Material preparation, data collection and analysis will be performed by SNL. The first draft of the manuscript will be written by SNL. All authors will read and approve the final manuscript.

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Figures

Figure 1

NovoTHOR bed. (Source of the image: NovoTHOR Photomedicine Ltd.)

Figure 2

NovoTHOR randomising switch box. (Source of the image: NovoTHOR Photomedicine Ltd.)

Figure 3

Flow diagram illustrating the assessments times.