

BMJ Open Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: protocol for a randomised placebo-controlled trial

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ABSTRACT

Introduction Low back pain (LBP) is one of the largest and most frequent public health problems worldwide. Photobiomodulation therapy (PBMT) is a frequently used non-pharmacological therapy for the treatment of musculoskeletal disorders. However, there is little high-quality scientific evidence that demonstrates the effectiveness of PBMT in the treatment of patients with chronic LBP in the short, medium and long term. Therefore, the objective of this clinical trial is to evaluate the effects of PBMT in patients with chronic non-specific LBP in the short, medium and long term.

Methods and analyses This is a prospectively registered, two-arm randomised placebo-controlled trial with blinded patients, assessors and treatment providers. One hundred and forty-eight patients with chronic non-specific LBP will be recruited. Treatment sessions will be provided three times a week for 4 weeks (totaling 12 sessions) with patients receiving either placebo or active PBMT. For ethical reasons, all patients, regardless of treatment allocation, will also receive an information booklet based on 'The Back Book'. Clinical outcomes will be measured at baseline, at the end of treatment, as well as 3, 6 and 12 months after randomisation. The primary outcomes will be pain intensity and disability measured after 12 sessions of treatment. The secondary outcomes will be pain intensity and disability measured at 3, 6 and 12 months after randomisation, in addition to specific disability and global perceived effect in all time points.

Ethics and dissemination The study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo. The results will be disseminated through scientific publications and presentations at national and international scientific meetings.

Trial registration number NCT03089424.

INTRODUCTION

Low back pain (LBP) is ranked as one of the most prevalent health problems and is highly associated with disability worldwide.¹⁻⁴ It is estimated that about 12% of the world's population suffer from LBP.⁵ Furthermore, LBP

Strengths and limitations of this study

- The present study can be considered to have high methodological quality since it is a randomised, controlled and prospectively registered clinical trial.
- One of the strengths of the study is that it is triple blinded, that is, outcome assessors, therapists and patients will be blinded to interventions over the course of the study.
- The sample size was calculated to provide the appropriate statistical power to detect precise differences for the primary outcomes of the study.
- In our study, we will test the effects of a single dose of photobiomodulation therapy (PBMT; ie, 24 Joules). PBMT is known to present a biphasic dose-response pattern, that is, within a therapeutic window (dosage range), the effects of biostimulation can be observed. However, if dosages below or above this window are used, these effects may not be observed. Therefore, the application of only one dose of PBMT may be considered a limitation of this trial. However to minimise this limitation, we based the choice of our parameters using the best available evidence.

generates high levels of work absenteeism and excessive costs to health systems.^{1,2} The prognosis of LBP is directly related to the duration of symptoms, with less favourable prognoses in patients with chronic LBP (ie, with a duration of symptoms longer than 3 months).⁶⁻¹⁰ Therefore, the ideal treatment for chronic LBP represents a significant challenge, since there are no treatments that cure persistent LBP. However, several interventions provide low to moderate effects in reducing pain and disability on this population.¹¹ The existing treatments for LBP can be divided into three categories: (1) pharmacological therapies, which trigger several adverse effects with prolonged use¹²⁻¹⁴; (2) non-pharmacological

therapies, which minimise undesirable effects and are moderately effective in LBP¹⁵ and surgery, used only when conservative treatment is not efficacious.¹⁶ Several therapies can be used to treat LBP by controlling symptoms, minimising disability and improving the patients' quality of life.¹⁷

Photobiomodulation therapy (PBMT) is a non-pharmacological intervention often used in the treatment of musculoskeletal disorders such as LBP.^{18–21} PBMT consists in applying a non-ionised form of light, which includes laser (light amplification by stimulated emission of radiation), light-emitting diodes and other lights with a broader spectrum ranging from visible to infrared.²² Recent evidence^{23–28} suggests that PBMT triggers positive physiological effects, such as increased microcirculation,²³ increased ATP synthesis,^{24 25} stimulation of the mitochondrial respiratory chain,^{24 25} stimulation of mitochondrial function²⁶ and factors that may influence the metabolism of various pathologies. In addition, there is evidence that PBMT reduces the release of both reactive oxygen species) and creatine kinase activity and also increases the production of antioxidants and heat shock proteins.^{27 28}

As PBMT has been successfully proven as an effective intervention for neck pain patients,²⁹ it is likely that PBMT could also be a reasonable option for patients with LBP. A range of previous trial have shown the effects of PBMT on acute, subacute and chronic LBP. Basford *et al*¹⁸ and Gur *et al*¹⁹ observed that PBMT appears to be effective in reducing pain and disability triggered by subacute and chronic LBP, respectively. While Konstantinovic *et al*²⁰ and Vallone *et al*²¹ found that PBMT combined with non-steroidal anti-inflammatory drugs (NSAIDs) and exercise were efficient in reducing pain intensity in patients with acute and chronic LBP, respectively. In a recent systematic review, Glazov *et al*³⁰ found a clinically significant reduction in pain intensity in chronic LBP in patients treated with PBMT, although a reliable conclusion was hindered by the high heterogeneity in the parameters of therapy application. Furthermore, a recent clinical practice guidelines³¹ recommended the use of the PBMT as a possible non-pharmacological treatment for chronic LBP. On the other hand, another trial³² did not detected differences between PBMT and placebo treatments on pain and disability in mixed sample of patients with acute and chronic LBP associated with lumbar disk degeneration. These findings show that there are still conflicts in the literature about PBMT in LBP. Therefore, high-quality and adequately powered trials are strongly needed.

Therefore, in spite of the positive results obtained in the aforementioned studies in favour of PBMT, some factors warrant further investigation with high-quality studies on the effects of PBMT applied in isolation in chronic non-specific LBP. Hence, it is necessary to conduct a high-quality, adequately powered, randomised placebo-controlled trial with outcomes have been measured at medium and long terms. Therefore, the objective of this study is to evaluate the effects of PBMT against placebo

in patients with chronic non-specific LBP in the short, medium and long term for the outcomes of pain intensity, general and specific disability and global perceived effect.

METHODS AND ANALYSES

Design

A randomised, triple-blinded (patients, therapists and outcome assessors), placebo-controlled trial will be performed. The protocol of this study has been prospectively registered on Clinicaltrials.gov (NCT03089424).

Study setting

The study will be conducted at the Centre for Excellence in Clinical Research in Physiotherapy of Universidade Cidade de São Paulo, Brazil.

Eligibility criteria

The study assessors will determine whether or not patients will be eligible to participate in the study based on patient history and clinical examination.

Inclusion criteria

- Patients with non-specific chronic LBP, defined as pain or discomfort between the costal margins and inferior gluteal folds with or without referred pain to the lower limbs;
- Persistent LBP for at least 3 months³³;
- Aged between 18 and 65 years;
- Both genders.

Exclusion criteria

- Patients with severe skin diseases (eg, skin cancer, erysipelas, severe eczema, severe dermatitis, severe psoriasis and severe hives lupus);
- Patients with LBP associated with nerve root compromise (measured by clinical examination of dermatomes, myotomes and reflexes)^{34 35};
- Serious spinal pathologies such as fractures, tumours, inflammatory and infectious diseases;
- Decompensated heart disease or metabolic disorders;
- Previous spinal surgery;
- Pregnancy.

Interventions

For ethical reasons, on the first day of treatment, all groups will receive an information booklet on LBP called 'The Back Book'³⁶ based on the recommendations of the European Guidelines.^{35 37} The booklet can be accessed freely via internet and it has been translated into Portuguese by our research team. At each treatment session, patients will receive further explanations on the contents of the booklet. There is consistent evidence that The Back Book is useful for patients with LBP³⁸ and it has been used in clinical trials conducted by our research group.^{39 40}

Patients will then be randomly allocated to two groups to be submitted to the active PBMT or placebo interventions. The active and placebo PBMT will be performed

using the same device and the irradiated sites will be the same in both therapies. To ensure blinding for therapists and patients, the device will emit the same sounds and the same information on the display regardless of the programmed mode (active or placebo). Furthermore, because the device produces a non-significant amount of heat,⁴¹ the patients will not be able to know if active or placebo PBMT will be administered. The device was previously coded as active or placebo modes, and only one researcher not involved in the randomisation, treatment and evaluation is aware of these codes. Patients will undergo treatment (active PBMT or placebo) according to prior randomisation, three times a week (with a minimal interval of 24 hours) for four consecutive weeks, totalling

12 therapy sessions. The choice of treatment frequency was based on Basford *et al.*¹⁸ The total treatment (active PBMT or placebo) time will be 27 min per patient. The patients will be positioned preferably in prone. However, in specific cases where patients do not tolerate this position due to pain, we will respect the patient's preferred positioning. Intervention specifications:

1. Active PBMT Group: The PBMT will be performed using the Multi Radiance Medical Super Pulsed Laser MR4 console (Solon, Ohio, USA), with the SE25 (emitter with an area of 4 cm²) and LaserShower (emitter with an area of 20 cm²) cluster probes as emitters. Nine sites will be irradiated on the patient's lumbar region. PBMT irradiation sites were chosen

Table 1 Parameters for SE25 and LaserShower cluster probe

	SE25	LaserShower
Number of lasers	1 super-pulsed infrared	4 super-pulsed infrared
Wavelength (nm)	905 (±1)	905 (±1)
Frequency (Hz)	3000	1000
Peak power (W)— each	25	12.5
Average mean optical output (mW)— each	7.5	1.25
Power density (mW/cm ²)—each	17.05	2.84
Energy density (J/cm ²)—each	3.07	0.511
Dose (J) - each	1.35	0.225
Spot size of laser (cm ²)—each	0.44	0.44
Number of red LEDs	4 red	4 red
Wavelength of red LEDs (nm)	640 (±10)	640 (±10)
Frequency (Hz)	2	2
Average optical output (mW)—each	15	15
Power density (mW/cm ²)—each	16.67	16.67
Energy density (J/cm ²)— each	3	3
Dose (J) - each	2.7	2.7
Spot size of red LED (cm ²)—each	0.9	0.9
Number of infrared LEDs	4 infrared	4 infrared
Wavelength of infrared LEDs (nm)	875 (±10)	875 (±10)
Frequency (Hz)	16	16
Average optical output (mW)—each	17.5	17.5
Power density (mW/cm ²)—each	19.44	19.44
Energy density (J/cm ²)—each	3.5	3.5
Dose (J)—each	3.15	3.15
Spot Size of LED (cm ²)—each	0.9	0.9
Magnetic field (mT)	35	35
Irradiation time per site (s)	180	180
Total dose per site (J)	24.75	24.30
Aperture of device (cm ²)	4	20
Application mode	Cluster probe held stationary in skin contact with a 90-degree angle and slight pressure	Cluster probe held stationary in skin contact with a 90-degree angle and slight pressure

LED, light-emitting diode.



Figure 1 Photobiomodulation therapy irradiation sites.

based on previous studies^{18–21} and to cover the largest possible area of the lumbar spine: three central sites on top of the spinous processes (between T11 and T12, L2 and L3, L5 and S1), using the SE25 (3000 Hz of frequency, 3 min of irradiation per site, 24.75 J per site, a totalising 74.25 J irradiated from SE25); in the same direction, but laterally, three sites on the left and three on the right (on the paravertebral muscles), using the LaserShower (1000 Hz of frequency, 3 min of irradiation per site, 24.30 J per site, a total of 145.80 J irradiated from LaserShower). At each treatment session, patients will receive a total dose of 220.05 J. At the end of the 12 treatments sessions, patients will receive a total dose of 2640.60 J. **Table 1** shows parameters for SE25 and LaserShower cluster probe. This PBMT application protocol was based on the study of Leal Junior *et al.*⁴²

2. Placebo PBMT Group: The placebo PBMT will be delivered using the same device that activates PBMT but without any emission of therapeutic dose. Patients will receive a total dose of 0 J in placebo mode. The placebo mode simulates the pragmatism of clinical practice and increases the credibility of the use of the equipment in relation to the treated patients. The placebo technique has already been widely used in other studies with patients with LBP,^{40 43–48} as well as in studies using PBMT.^{41 49 50}

Figure 1 shows the PBMT irradiation sites.

We will use two different emitters in PBMT (active or placebo) because we have different objectives in each application area, which consequently require different mechanisms of action. We will use the SE25 emitter on the spinous processes to inhibit pain. Considering the smaller area of this emitter (4 cm²), the power density will be increased, which will consequently induce the triggering of inhibitory effects, such as a decrease in the axonal flow and thus analgesic effects.^{51 52} In addition, the higher frequency used in this emitter will also increase the number of photons that will reach the target tissue, which will also promote the triggering of inhibitory effects and consequent analgesic effect. For the erector spinae muscles, we will use the LaserShower 50 (LS50) emitter to promote photobiostimulatory effects, considering the larger area of the device (20 cm²), with consequent lower power density. In addition, this emitter has a lower frequency, which will consequently decrease the number of photons delivered to the target tissue. With these factors, we believe that we will promote an increase in the production of ATP,^{24 25} an increase in microcirculation²³ and consequently a decrease in muscle fatigue and stiffness. This therapeutic strategy using different emitters and different frequencies showed positive effects in the reduction of non-specific knee pain in a previous study that used this same PBMT device and these same emitters⁴²; however, the frequencies and doses were adapted for back pain patients.

Outcomes and blinding

Primary outcomes of the study will be obtained at baseline and immediately after the last treatment session (4 weeks). Secondary outcomes of the study will be obtained at baseline, at the end of treatment (4 weeks) and 3, 6 and 12 months after randomisation. These outcomes will be collected by an assessor who will not be aware of patient allocation to their treatment groups.

The primary outcomes of the study will be

- Pain intensity measured by the Pain Numerical Rating Scale.⁵³ Pain Numerical Rating Scale evaluates pain intensity levels perceived by the patient on an 11-point scale ranging from 0 to 10, with 0 being 'no pain' and 10 'the worst possible pain'.⁵³ Patients will be instructed to score the level of pain intensity based on the last 7 days.
- Disability associated with LBP, as measured by the Roland-Morris Disability Questionnaire.^{54 55} The questionnaire consists of 24 items that describe situations that patients may have difficulty performing on a daily basis due to LBP. The greater the number of affirmative answers is, the higher the level of functional disability associated with LBP.^{53 55} Patients will be instructed to answer according to their condition on the day of administration of the questionnaire.

The secondary outcomes of the study will be

- Specific disability, as measured by the Patient-Specific Functional Scale.⁵³ The Patient-Specific Functional

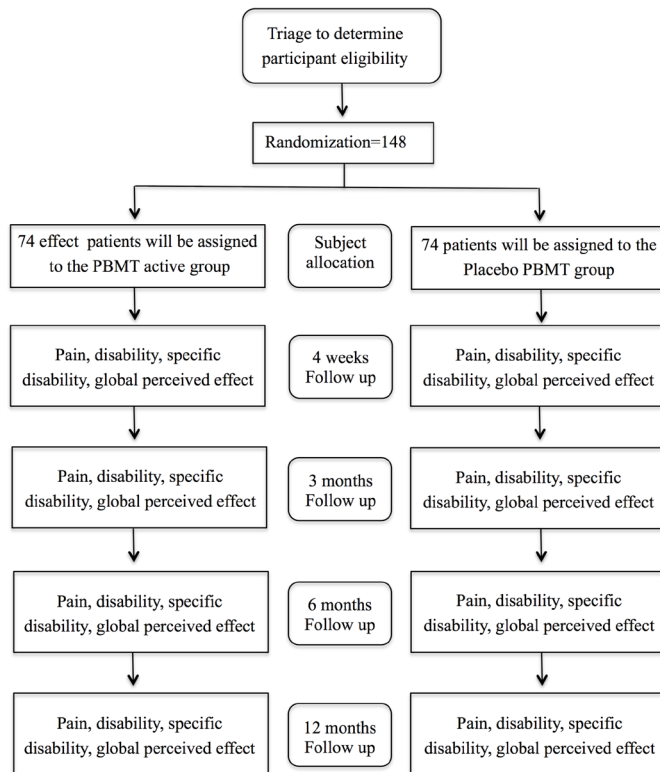


Figure 2 Flow diagram of the study. PBMT, photobiomodulation therapy.

Scale is global and can be used for any part of the body. The measurement is done on an 11-point Likert scale for each activity, and the higher the average score is (ranging from 0 and 10 points), the better the patient's ability to perform the activities. The patients will be asked to identify up to three activities that they consider they are incapable of performing or that they have some difficulty performing.^{53 56 57}

- Global perceived effect as measured by the Global Perceived Effect Scale.⁵³ Global Perceived Effect Scale is an 11-point Likert scale, ranging from -5 to +5, that compares the patient's current condition to the onset of symptoms.⁵³ Positive scores represent improvement, while the negative scores represent worsening in relation to the onset of symptoms. Values closer to 5 mean greater intensity of this perception.⁵³
- Pain intensity measured by the Pain Numerical Rating Scale.⁵³
- Disability associated with LBP, as measured by the Roland-Morris Disability Questionnaire.^{54 55}

Participant timeline

The Consolidated Standards of Reporting Trials flow-chart summarising experimental procedures and patients are shown in [figure 2](#).

Sample size

The sample calculation of the study was performed to detect a 1-point difference for the outcome pain intensity (as measured by the Pain Numerical Rating Scale),⁵³ with an estimated SD of 1.84 points and 4 points for the

outcome disability associated with LBP (measured by the Roland-Morris Disability Questionnaire),^{54 55} with an estimated SD of 4.9 points. A statistical power of 80% was considered for the two outcomes, with α of 5% and a possible sample loss of up to 15%. Therefore, a total of 148 patients will be required for the study.

Recruitment

Patients seeking treatment for chronic LBP will be recruited at primary or secondary care health services. We will partner with supervising clinicians at primary and secondary health services so that they will refer chronic non-specific LBP patients to our study for treatment.

Randomisation

Prior to initiation of treatment, patients will be randomised into their respective intervention groups. The randomisation will be generated by a computer program (Excel Office 2010) and performed by a participating researcher not involved with the recruitment or evaluation of patients. This same researcher will be responsible for programming the PBMT device according to the result of the randomisation. The PBMT device used in the present study will make the same sounds regardless of the programmed dose and mode (active PBMT or placebo PBMT). This researcher will be instructed not to disclose the programmed intervention to the therapist or any of the patients and other researchers involved in the study until its completion. Patient and therapist will be blinded throughout the treatment. Concealed allocation will be achieved through the use of sequentially numbered, sealed and opaque envelopes.

Data collection

The patients will be welcomed by the study's blinded assessor who will determine whether they will be eligible to participate in the study. Subsequently, a file will be completed with the patient's sociodemographic data and clinical history. Next, the primary outcomes and the secondary outcomes of the study will be collected. Then, all eligible patients will be randomised and allocated into two treatment groups: active PBMT or placebo PBMT. At the end of the 12 treatment sessions, the primary and secondary outcomes of the study participants will be reassessed by the same evaluator who performed the baseline assessment. The 3, 6 and 12-month follow-ups will be performed by telephone by the same evaluator who carried out the other evaluations. All of the questionnaires that will be used in the present study have been fully tested for their measurement properties.^{53 55} These measurement properties were also tested over the phone. Therefore, we are confident that the assessments are reliable.

Statistical analysis

The statistical analysis will be conducted following the principles of intention-to-treat analysis.⁵⁸ The normality of the data will be tested by visual inspection of histograms and the characterisation of the participants will be

calculated using descriptive statistical tests. The between-group differences (treatment effects) and their respective 95% CIs will be calculated by using mixed linear models⁵⁹ using the group-by-time interaction terms. The analyses will be performed using SPSS V.19.

Ethics

The present study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo under number 1.964.094. All patients eligible for the study will be informed by study assessors of the objectives and will be required to complete the informed consent form (see online supplementary appendix 1), as determined by Brazilian National Health Council Resolution 196/96.

Research personnel will take all appropriate and customary steps to ensure that data remain secure and that patient privacy and confidentiality will be maintained.

Dissemination policy

The study will be disseminated through publication in peer-reviewed international journals, as well as presentations at national and international conferences.

DISCUSSION

Chronic LBP is a condition that is often associated with disability, emotional alterations and absenteeism from work.⁸ Since chronic LBP is very prevalent,¹¹ it has a great financial impact, generating high costs, both direct and indirect.⁶⁰ This fact demonstrates the importance of the constant investigation of more suitable treatments for LBP, aiming at the well-being of the patient and the reduction of expenses for health systems.

PBMT is one of the interventions recommended for the treatment of chronic LBP,³¹ however, it is a relatively recent therapy given that the first clinical trial investigating its effects on LBP was published in 1999.¹⁸ Since then, there are still conflicts in the literature about PBMT in LBP. Although there is evidence that PBMT is no better than placebo treatment on pain and disability in a mixed sample of patients with acute and chronic LBP,³² some studies have demonstrated the efficacy of PBMT in chronic and acute LBP.^{18–21} Nevertheless, there are still issues to be clarified about its efficacy, as there are no high-quality methodological studies that test PBMT versus placebo in LBP patients. To date, studies evaluating the effects of PBMT on chronic non-specific LBP have not been prospectively registered^{18–21}; have a small sample size^{18–21} and have high risk of bias. In addition, none of the studies were either triple blinded or were analysed using intention-to-treat principles.

It is extremely important to carry out studies with high methodological quality aimed at contributing to a better understanding of the effects of PBMT on LBP. Only then will it be possible to determine whether PBMT can be used as one of the treatments of choice for LBP. If the effectiveness of PBMT in LBP is confirmed, it could be used as an alternative method to NSAIDs or opioids, for example,

since it causes similar or superior effects to these drugs, shown in other chronic musculoskeletal disorders,^{61–62} without the presence of known adverse effects at present. We believe that, by providing relevant and compelling information about PBMT, we will contribute to a safer and more effective clinical practice.

Nevertheless, it is important to highlight that PBMT presents a biphasic dose–response pattern, that is, within a therapeutic window (dose range) the biostimulation effects can be seen. Very low doses may not trigger responses in the irradiated tissue, whereas very high doses may cause inhibition.⁵² In addition, the power and time of irradiation are also extremely important parameters to obtain better results with the PBMT.⁶³ Therefore, the choice of PBMT parameters is essential for obtaining positive results and represents an important challenge in treating any musculoskeletal disorder. To date, there is great heterogeneity in the parameters of PBMT used for the treatment of LBP, and it is not possible to conclude the best dose for the treatment of this disorder. Thus, our parameters were adapted from the best evidence available⁴² and took into consideration the dosage recommended by World Association for Laser Therapy.⁶³ Therefore, although we believe that the dosage chosen for the present study is the most likely to be effective in triggering the expected results, a limitation of our study is that we will test only one dose of PBMT.

The present study can be considered to have high methodological quality, since it is a randomised, controlled and prospectively registered clinical trial. In addition, one of the strengths of the study is that it is triple blinded, that is, evaluators, therapists and patients will be blinded to interventions over the course of the study. Finally, the sample size was calculated to provide the appropriate statistical power to detect precise differences in the primary outcomes of the study. Therefore, we believe that this study will contribute to the evidence-based practice of PBMT in patients with chronic LBP.

Contributors SST and LOPC contributed to the concept and design of the study and established the hypothesis and wrote the original proposal. SST, LCMC, LSG, ACA, DPN, FCM, MAA and LOPC contributed significantly in creating the manuscript. LCMC and LOPC performed critical revisions of the manuscript. SST, LCMC and LOPC wrote the final version of the manuscript. All authors read and approved the final version of the manuscript.

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