




# Photobiomodulation Therapy is Able to Modulate PGE<sub>2</sub> Levels in Patients With Chronic Non-Specific Low Back Pain: A Randomized Placebo-Controlled Trial

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**Background and Objectives:** Non-specific low back pain (LBP) is responsible for triggering increased biomarkers levels. In this way, photobiomodulation therapy (PBMT) may be an interesting alternative to treat these patients. One of the possible biological mechanisms of PBMT involved to decrease pain intensity in patients with musculoskeletal disorders is modulation of the inflammatory mediators' levels. The aim of this study was to evaluate the effects of PBMT compared with placebo on inflammatory mediators' levels and pain intensity in patients with chronic non-specific LBP.

**Study Design/Materials and Methods:** A prospectively registered, randomized triple-blinded (volunteers, therapists, and assessors), placebo-controlled trial was performed. Eighteen patients with chronic non-specific LBP were recruited and treated with a single session of active PBMT or placebo PBMT. The primary outcome of the study was serum prostaglandin E<sub>2</sub> levels and the secondary outcomes were tumor necrosis factor- $\alpha$ , interleukin-6 levels, and pain intensity. All outcomes were measured before and after 15 minutes of treatment session.

**Results:** PBMT was able to decrease prostaglandin E<sub>2</sub> levels at post-treatment compared with placebo, with a mean difference of  $-1470$  pg/ml, 95% confidence interval  $-2906$  to  $-33.67$  in patients with LBP. There was no difference between groups in the other measured outcomes. Patients did not report any adverse events.

**Conclusion:** Our results suggest that PBMT was able to modulate prostaglandin E<sub>2</sub> levels, indicating that this may be one of the mechanisms involved in the analgesic effects of PBMT in patients with LBP. Trial registration number (ClinicalTrials.gov): NCT03859505. Lasers Surg. Med. © 2020 The Authors. Lasers in Surgery and Medicine published by Wiley Periodicals, Inc.

**Key words:** low-level laser therapy; inflammatory mediators; low back pain; musculoskeletal disorders; physical therapy; rehabilitation.

## INTRODUCTION

Low back pain (LBP) is a very common musculoskeletal condition worldwide, affecting people of all ages [1], being the major cause of disability globally [2]. Most patients with an acute episode of LBP recover within 6 weeks [3], nevertheless, 67% of the patients still report pain at 3 months and 65% at 12 months, developing chronic LBP [3,4]. LBP is thought to be triggered by several risk factors

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such as psychosocial [5], other chronic diseases [6], sleep disorders [6], and physical stress [7], for example. However, in about 90–95% of the cases the cause of the pain cannot be identified, and these patients are classified as having non-specific LBP [8,9].

Over the past years, research has been conducted to investigate the presence and increase of inflammatory mediators in different painful musculoskeletal disorders [10–15]. These studies [10–15] observed changes in some biomarkers, in plasma or microdialysate, indicating that patients with LBP might also present changes at inflammatory mediators' levels [16,17]. Increased knowledge about the aspects behind non-specific LBP may help to improve the diagnosis, management, and treatment of these patients [17]. In this way, a novel area of research has been developed to investigate the role of inflammatory mediators in LBP. So far, few studies have been conducted, and there is still conflicting evidence on this topic [18]. However, studies have observed increased plasmatic levels of inflammatory mediators (e.g., tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], interleukin-6 [IL-6], IL-1 $\beta$ , and prostaglandins) in patients with non-specific LBP [19–23].

There are many interventions available to treat patients with non-specific LBP [9], and the current focus is on self-management, physical and psychological therapies, and less focus on pharmacological treatment and surgery [24]. Photobiomodulation therapy (PBMT) has been widely used to manage different musculoskeletal disorders such as non-specific knee pain, temporomandibular disorders, fibromyalgia, osteoarthritis, and neck pain [25–29]. In addition, PBMT is a non-invasive treatment for LBP recommended by the American College of Physicians' clinical practice guidelines [30].

One of the possible biological mechanisms of PBMT involved in decrease pain intensity in musculoskeletal disorders is modulating the inflammatory mediators' levels [31]. Over the past years, evidence from preclinical studies have shown positive effects of PBMT on modulating different inflammatory mediators such as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 in different musculoskeletal disorders [32–37]. However, there is a lack of both preclinical studies and randomized controlled trials investigating the effects of PBMT on inflammatory mediators in LBP. In addition, the role of modulation through PBMT of these inflammatory mediators and consequent decrease of pain intensity is not well-understood.

We hypothesized that PBMT would be able to decrease the inflammatory mediators' levels, especially PGE<sub>2</sub>, in patients with chronic non-specific LBP compared with placebo. In addition, this modulatory effect might be one of the mechanisms involved in the analgesic effects of PBMT in patients with LBP. Therefore, this study aimed to evaluate the acute effects of PBMT compared with placebo on systemic inflammatory mediators' levels (PGE<sub>2</sub>, TNF- $\alpha$ , and IL-6) and pain intensity in patients with chronic non-specific LBP.

## MATERIALS AND METHODS

### Design

A prospectively registered (NCT03859505), two-arm, parallel randomized, triple-blinded (patients, therapists, and outcome assessors), placebo-controlled trial was conducted. All methodological steps of this study are described in detail in the published protocol [38]. There were no deviations from the registered protocol.

### Ethics

This study was submitted and approved by the Regionale Komiteer for Medisinsk og Helsefaglig Forskningsetikk (number 2018/1361/REK Nord). All patients eligible for the study were informed by study assessors of the objective and were required to complete the consent form.

### Participants and Recruitment

We recruited a total of 18 patients with non-specific chronic LBP. The participants were recruited from the university staff and students between March and April 2019.

### Eligibility Criteria

The study assessors determined whether or not the patients were 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 in the lower limbs;
- Persistent LBP for at least 3 months [39];
- Pain intensity of at least 3 points, measured by Pain Numerical Rating Scale [40];
- Aged between 18 and 65 years;
- Any gender.

Exclusion criteria:

- Patients with severe skin diseases (e.g., skin cancer, erysipelas, severe eczema, severe dermatitis, severe psoriasis, and severe hives lupus) [41];
- Patients with LBP associated with nerve root compromise (measured by clinical examination of dermatomes, myotomes, and reflexes) [42,43];
- Serious spinal pathologies such as fractures, tumors, inflammatory and infectious diseases;
- Decompensated heart disease or metabolic disorders;
- Previous spinal surgery;
- Pregnancy.

### Randomization and Blinding

Prior to initiation of the treatment, patients were randomized into their respective intervention groups: active PBMT or placebo-control. The randomization was generated by a computer program (Excel Office 2010)



Fig. 1. Treatment irradiation sites.

and performed by a participating researcher not involved with the recruitment or treatment of patients. This same researcher was responsible for programming the PBMT device according to the result of randomization, as active or placebo mode. This researcher was instructed not to disclose the programmed intervention to the assessor, therapist, or any of the patients and other researchers involved in the study until its completion. The assessor, patients, and the therapist were blinded throughout the treatment. Concealed allocation was achieved through the use of sequentially numbered, sealed, and opaque envelopes.

### Interventions

Patients were randomly allocated into two groups to be submitted to the active PBMT or placebo interventions. The active and placebo PBMT were performed using the same device and the irradiated sites were the same in both therapies (Fig. 1). To ensure blinding for therapists and patients, the device emitted 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 [44], the patients were not able to know if active or placebo PBMT were administered.

Patients underwent treatment (active PBMT or placebo) according to prior randomization in a single session. Intervention specifications are:

1. Active PBMT group: The PBMT was performed using the Multi Radiance Medical Super Pulsed Laser MR4 console (Solon, OH), with SE25 (emitter with an area of 4 cm<sup>2</sup>, 3000 Hz of frequency, 3 minutes of irradiation per site, 24.74 J per site, a total of 74.25 J irradiated from SE25) and LaserShower (emitter with an area of 20 cm<sup>2</sup>, 1000 Hz of frequency, 3 minutes of irradiation per site, 24.30 J per site, a total of 145.80 J irradiated from LaserShower) cluster probes as emitters. Nine sites were irradiated on the patient's lumbar region: three central sites on top of the spinous processes (between T11 and T12, L2 and L3, L5 and S1), using the SE25; in the same direction, but laterally, three sites on the left and three on the right (on the paravertebral muscles), using the LaserShower (LS). PBMT irradiation sites were chosen based on a previous study [41] and to cover the largest possible area of the low back [45] (Fig. 1). The treatment was performed in a single session and patients received a total of 220.05 J. This PBMT application protocol was based on the previous study [41]. The PBMT parameters were previously optimized in feasibility studies performed by the manufacturer. Table 1 shows the PBMT parameters.
2. Placebo-control group: The placebo-control was delivered using the same device as that of active PBMT but without any emission of therapeutic dose. Moreover, the irradiated sites and the irradiation time were the same as that of active PBMT. Patients received a total dose of 0 J in the placebo mode. This treatment was also performed in a single session.

### Procedures

The patients were welcomed by the study's blinded assessor who determined whether they were eligible to participate in the study. Subsequently, a file was completed with the patient's sociodemographic data and clinical history. Next, the 0-10 Pain Numerical Rating Scale measuring the pain intensity and blood sample collection for analysis of inflammatory mediators were performed in all eligible patients. Then, all the eligible patients were randomized and allocated into two treatment groups: active PBMT and placebo-control. After 15 minutes of the only treatment session the intensity of pain and blood sample were collected again. Blood samples at baseline and at the end of treatment were collected by a qualified nurse blinded to group allocation and were obtained from an antecubital vein. One hour after collection, each sample was centrifuged at 3000 rpm for 20 minutes. Pipettes were used to transfer the serum to Eppendorf® tubes, which were stored at -80°C until analysis.

### Outcomes

Demographic and clinical characteristics (e.g., age, duration of symptoms, weight, height, and use of medication) were assessed at baseline. Clinical and biochemical outcomes were obtained at baseline and 15 minutes after the only treatment session by an assessor who was unaware of the patients' allocation to their treatment groups. The primary outcome was PGE<sub>2</sub> levels at the end of treatment, since it is a lipid mediator that contributes to inflammatory pain [46]. The secondary outcomes were TNF-α and IL-6 levels, besides pain intensity at the end of treatment. The inflammatory mediators' levels (PGE<sub>2</sub>, TNF-α, and IL-6) were measured by enzyme-linked immunosorbent assay (ELISA) method,

**TABLE 1. PBMT parameters**

	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 <sup>2</sup> )—each	17.05	2.84
Energy density (J/cm <sup>2</sup> )—each	3.07	0.511
Dose (J)—each	1.35	0.225
Spot size of laser (cm <sup>2</sup> )—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 <sup>2</sup> )—each	16.67	16.67
Energy density (J/cm <sup>2</sup> )—each	3	3
Dose (J)—each	2.7	2.7
Spot size of red LED (cm <sup>2</sup> )—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 <sup>2</sup> )—each	19.44	19.44
Energy density (J/cm <sup>2</sup> )—each	3.5	3.5
Dose (J)—each	3.15	3.15
Spot Size of LED (cm <sup>2</sup> )—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 <sup>2</sup> )	4	20
Application mode	Cluster probe held stationary in skin contact with a 90° angle and slight pressure	Cluster probe held stationary in skin contact with a 90° angle and slight pressure

LED, light-emitting diode.

using a commercial kit and following the manufacturer's instructions (BD Biosciences®, Franklin Lakes, NJ). Spectrophotometric readings were performed in a SpectraMax® Plus 384 Absorbance Plate Reader (Sunnyvale, CA) with 450-nm wavelength and correction to 570 nm. The results were expressed in pg/ml. Pain intensity was measured by the Pain Numerical Rating Scale [40], that 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” [40]. Patients were instructed to score the level of pain intensity based at the time of evaluation.

### Characterization of Sample

As no studies assessing the effects of PBMT on inflammatory mediators in patients with non-specific LBP are available, the number of patients per group in the present study was calculated based on a pilot study. This pilot study was recently conducted by our research group with three patients per group in order to estimate the

sample size. A  $\beta$  value of 20% and a  $\alpha$  of 5% were used to calculate the sample size. The pilot study showed that applying PBMT in patients with non-specific LBP resulted in levels of PGE<sub>2</sub> (primary outcome of the present study) post-treatment of 1.05 pg/μl (0.42 standard deviation), whereas applying the placebo in patients with non-specific LBP resulted in levels of PGE<sub>2</sub> post-treatment of 1.52 pg/μl (0.39 standard deviation). We used the Researcher's Toolkit to calculate the sample size (<https://www.dssresearch.com/resources/calculators/sample-size-calculator-average>). On the basis of the aforementioned parameters used to calculate the sample, we found a sample of 9 patients per group, for a total of 18 patients.

### Statistical Analysis

The statistical analysis followed intention-to-treat principles (i.e., the participants were analyzed in the groups to which they were allocated) [47]. The characteristics of the participants were presented using descriptive

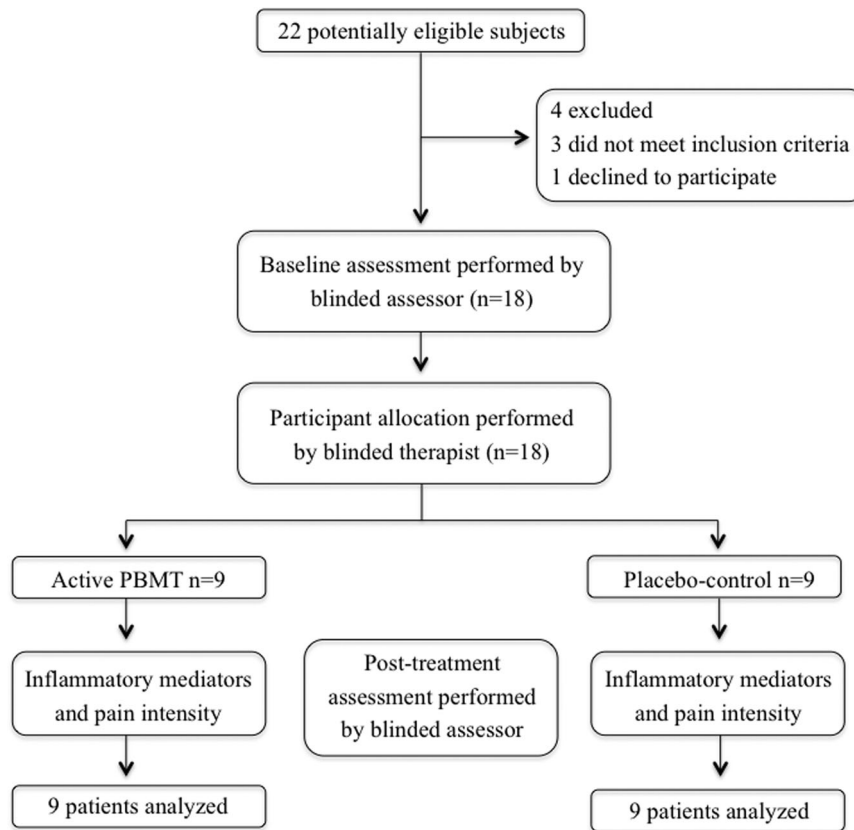


Fig. 2. Flow diagram of the study. PBMT, photobiomodulation therapy.

**TABLE 2. Demographic and Clinical Characteristics of the Patients at Baseline (n = 18)**

Variables	Active PBMT (n = 9)	Placebo-control (n = 9)
Gender		
Female	5 (55.56)	6 (66.67)
Male	4 (44.44)	3 (33.33)
Age	33.78 (13.27)	31.44 (12.79)
Duration of symptoms (weeks)	82.67 (68.53)	82.67 (95.71)
Weight (kg)	80.33 (14.16)	77.44 (16.21)
Height (cm)	170.11 (8.43)	168.89 (9.14)
Marital status		
Single	4 (44.44)	5 (55.56)
Married	4 (44.44)	4 (44.44)
Divorced	1 (11.11)	0 (0.00)
Use of medication (NSAIDs and analgesics)	5 (55.56)	5 (55.56)
Pain intensity (0-10)	6.44 (1.74)	6.44 (1.42)
PGE2 levels (pg/ml)	5430.99 (1419.58)	5655.46 (914.14)
TNF- $\alpha$ (pg/ml)	365.82 (0.21)	365.84 (0.32)
IL-6 (pg/ml)	145.72 (0.58)	145.81 (0.58)

Categorical variables are expressed as number (%), continuous variables are expressed as mean (SD).

IL-6, interleukin-6; NSAIDs, non-steroidal anti-inflammatory drugs; PBMT, photobiomodulation therapy; PGE2, prostaglandin E<sub>2</sub>; SD, standard deviation; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

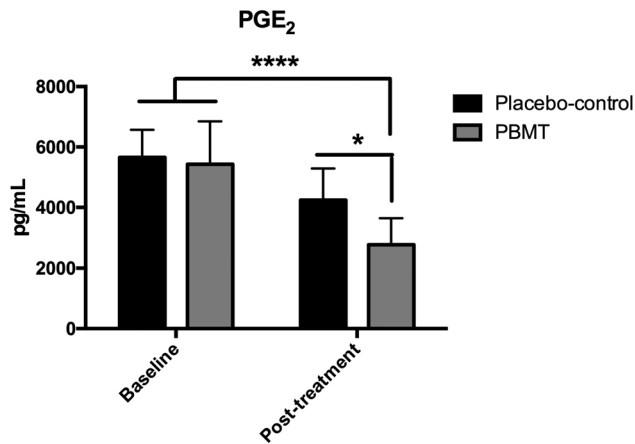


Fig. 3. Levels of PGE<sub>2</sub>. Data are expressed as mean and standard deviation. \* $P = 0.04$ , \*\*\*\* $P < 0.0001$ . PBMT, photobiomodulation therapy.

statistical tests. The findings were tested for their normality using the Shapiro–Wilk test. The between-group differences and their respective 95% confidence interval (CIs) were calculated by two-way repeated-measures (ANOVA, time vs. experimental group) with post hoc Bonferroni correction. The significance level was set at  $P < 0.05$ . The data were expressed as mean and standard deviation.

## RESULTS

### Recruitment and Baseline Data

From a total of 22 patients with LBP comprising university staff and students, 18 were considered eligible and were included in the study between March 2019 and April 2019 (Fig. 2). The baseline characteristics of both groups were similar, as described in Table 2. Most of the study participants were women, married, and the average age was 32.6 years.

### Primary Outcome

There were no differences between groups at baseline ( $P > 0.05$ ). Patients allocated to the active PBMT group had decreased PGE<sub>2</sub> levels ( $P = 0.04$ ) with a mean difference of  $-1470$  (95% CI  $-2906$  to  $-33.67$ ) compared with placebo-control group at post-treatment (Fig. 3).

### Secondary Outcomes and Estimation/Adverse Events

There were no statistically significant differences ( $P > 0.05$ ) for the TNF- $\alpha$  levels with a mean difference of  $-0.16$  (95% CI  $-0.52$  to  $0.20$ ), IL-6 levels with a mean difference of  $0.01$  (95% CI  $-0.91$  to  $0.93$ ), and pain intensity with a mean difference of  $-0.66$  (95% CI  $-2.62$  to  $1.30$ ) between PBMT and placebo-control at post-treatment (Fig. 4). Furthermore, patients did not report any adverse events.

## DISCUSSION

To the best of our knowledge, this is the first randomized placebo-controlled trial aiming to evaluate the acute

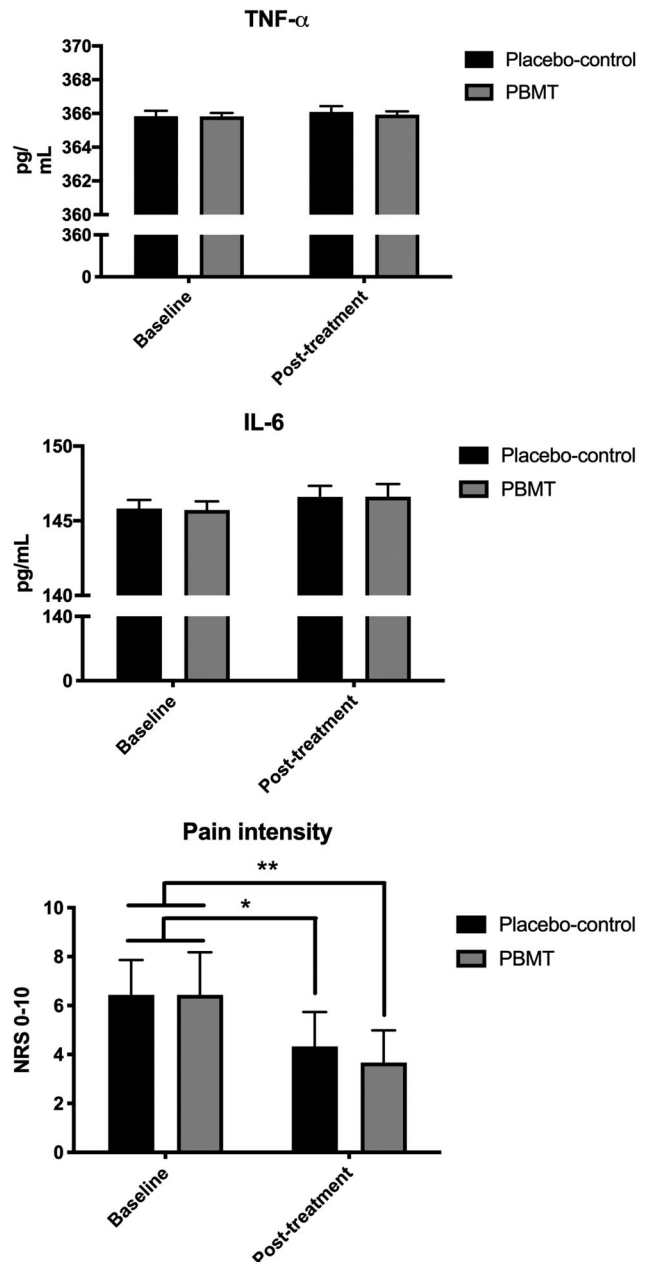


Fig. 4. Levels of TNF- $\alpha$ , IL-6, and pain intensity. Data are expressed as mean and standard deviation. \*\* $P < 0.0023$ , \* $P < 0.029$ . IL-6, interleukin-6; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

effects of PBMT on systemic levels of inflammatory mediators in patients with chronic non-specific LBP. We observed that a single session of PBMT was able to decrease the PGE<sub>2</sub> levels when compared with placebo-control, suggesting that PBMT can modulate inflammation in patients with chronic non-specific LBP. On the contrary, the TNF- $\alpha$  and IL-6 levels remained unchanged, indicating that a single session of PBMT was not effective in decreasing these pro-inflammatory cytokine levels.

Finally, a single session of PBMT was not enough to decrease pain intensity in patients with LBP.

There is a considerable amount of evidence regarding the positive effects of PBMT on inflammatory mediators in preclinical studies. PBMT was able to modulate inflammation by inhibiting cyclooxygenases 2, and consequently decreasing PGE<sub>2</sub> levels in cell culture [48]. Moreover, PBMT was able to decrease PGE<sub>2</sub> levels and other inflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 in experimental models of osteoarthritis, muscle injury, muscular dystrophies, and tendinopathies [32–37], for example. On the contrary, there is still a dearth of well-conducted randomized controlled trials investigating the effects of PBMT on musculoskeletal disorders. Previous studies have observed that PBMT was able to decrease pain in patients with non-specific knee pain [25], temporomandibular disorders [26], fibromyalgia [27], osteoarthritis [28], and neck pain [29]. However, in these studies only clinical outcomes were measured and the possible biological mechanism involved in the positive effects observed with PBMT was not investigated.

A previous controlled trial observed that PBMT was able to decrease PGE<sub>2</sub> levels in Achilles tendinitis [31], corroborating our results. These findings may suggest that PBMT is effective in modulating inflammatory processes in different tissues and conditions, not only in experimental models, but also in humans. The results of our study are compatible with the hypothesis that modulating inflammation by decreasing PGE<sub>2</sub> levels may be one of the mechanisms involved in the effects of PBMT in musculoskeletal disorders. It is known that increased levels of PGE<sub>2</sub> sensitize nociceptors, leading to increased pain hypersensitivity [49]. Thus, a decrease in these eicosanoid levels might contribute to the reduction of pain in patients with LBP, also by decreasing pain sensitivity.

In our randomized controlled trial, we observed decrease of pain intensity in patients with LBP in both groups. However, the reduction was similar in both PBMT and placebo-control patients. This finding may suggest that since the sample size was calculated to provide appropriate statistical power to detect precise differences for the primary outcome of the study (PGE<sub>2</sub>), it is very likely that no statistical power has been achieved to detect differences for the secondary outcomes. Possibly a larger sample size would be necessary to detect the differences in pain intensity. In addition, non-specific LBP is a multifactorial condition, and a decrease in inflammatory mediators' levels (such as PGE<sub>2</sub>) with a single treatment using PBMT may not be enough to decrease pain intensity.

To date, the optimal time-response window for the use of PBMT in musculoskeletal conditions such as LBP has not been established, however, experimental studies have shown a decrease in TNF- $\alpha$  and IL-6 levels from 5 to 24 hours after PBMT [32–37]. Although we did not observe changes in TNF- $\alpha$  and IL-6 levels, it is important to highlight that analyses were performed in only one time point, 15 minutes after treatment. Therefore, we may

suggest that the decrease of these inflammatory mediators might take longer to be detected in blood stream. Finally, we cannot rule out the involvement of other mechanisms of PBMT that were not investigated in this trial.

Our study is the pioneer in investigating the effects of PBMT on inflammatory mediators' levels in patients with LBP. Thus, it is important that further studies be carried out to investigate the role of other inflammatory mediators in this disorder. In addition, although the observed outcomes are promising, indicating that patients with LBP may benefit from the use of PBMT, it is needed that further studies emphasize clinical and relevant outcomes for patients. Our study is important to elucidate one possible mechanism of action of PBMT in patients with LBP for the scientific community. Our findings also can be helpful as a starting point for further studies that should focus on patient-centered outcomes. For such, a larger sample size probably should be necessary. Finally, further studies are needed to optimize parameters and to establish the time-response window for PBMT, testing different timepoints, to achieve better results.

Limitations of our study include to have used only a short-term follow-up of 15 minutes after one single treatment session. On the contrary, the strengths of our study include the originality of the investigated topic and high methodological quality (i.e., randomized controlled trial, triple-blinded design, and prospectively registered). Moreover, the sample size was calculated to provide the appropriate statistical power to detect precise differences for the primary outcome of the study (PGE<sub>2</sub> levels) and possibly the sample size was not powered enough to detect differences for the secondary outcomes.

## CONCLUSION

Our results suggest that PBMT was able to modulate PGE<sub>2</sub> levels. Thus, the results of our study are compatible with the hypothesis that modulating inflammation by decreasing PGE<sub>2</sub> levels may be one of the mechanisms involved in the effects of PBMT in patients with LBP.

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