Lasers in Medical Science (2019) 34:711–719
https://doi.org/10.1007/s10103-018-2645-z

ORIGINAL ARTICLE

Acute effects of photobiomodulation therapy (PBMT) combining laser diodes, light-emitting diodes, and magnetic field in exercise capacity assessed by 6MST in patients with COPD: a crossover, randomized, and triple-blinded clinical trial

Eduardo Foschini Miranda[1] · Welton Alves Diniz[1] · Marcos Vinicius Nogueira Gomes[1] · Marcelo Ferreira Duarte de Oliveira[1,2] · Paulo de Tarso Camillo de Carvalho[1] · Ernesto Cesar Pinto Leal-Junior[1,2]

Received: 29 January 2018 / Accepted: 18 September 2018 / Published online: 25 September 2018

Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by dyspnea, as well as musculoskeletal and systemic manifestations. Photobiomodulation therapy (PBMT) with use of low-level laser therapy (LLLT) and/or light-emitting diode therapy (LEDT) is an electrophysical intervention that has been found to minimize or delay muscle fatigue. The aim of this study was to evaluate the acute effect of PBMT with combined use of lasers diodes, light-emitting diodes (LEDs), magnetic field on muscle performance, exercise tolerance, and metabolic variables during the 6-minute stepper test (6MST) in patients with COPD. Twenty-one patients with COPD (FEV_1 46.3% predicted) completed the 6MST protocol over 2 weeks, with one session per week. PBMT/magnetic field or placebo (PL) was performed before each 6MST (17 sites on each lower limb, with a dose of 30 J per site, using a cluster of 12 diodes 4 × 905 nm super-pulsed laser diodes, 4 × 875 nm infrared LEDs, and 4 × 640 nm red LEDs; Multi Radiance Medical™, Solon, OH, USA). Patients were randomized into two groups before the test according to the treatment they would receive. Assessments were performed before the start of each protocol. The primary outcomes were oxygen uptake and number of steps, and the secondary outcome was perceived exertion (dyspnea and fatigue in the lower limbs). PBMT/magnetic field applied before 6MST significantly increased the number of steps during the cardiopulmonary exercise test when compared to the results with placebo (129.8 ± 10.6 vs 116.1 ± 11.5, $p = 0.000$). PBMT/magnetic field treatment also led to a lower score for the perception of breathlessness (3.0 [1.0–7.0] vs 4.0 [2.0–8.0], $p = 0.000$) and lower limb fatigue (2.0 [0.0–5.0] vs 4.0 [0.0–7.0], $p = 0.001$) compared to that with placebo treatment. This study showed that the combined application of PBMT and magnetic field increased the number of steps during the 6MST and decreased the sensation of dyspnea and lower limb fatigue in patients with COPD.

Keywords Low-level laser therapy · Light-emitting diode therapy · Phototherapy · Performance · COPD · 6MST

Introduction

Chronic obstructive pulmonary disease (COPD) is a characterized by dyspnea, as well as musculoskeletal and systemic manifestations [1]. Because of the primary site affected by COPD, reduced functional capacity has for many decades been attributed to changes in respiratory mechanics and impaired pulmonary gas exchange, resulting in dyspnea being the principal symptom limiting exercise [2, 3].

Structural changes in the lower limb muscles result in reduced overall exercise capacity, progressing to deconditioning caused by a reduction in the performance of physical activities of daily living [4, 5]. Gosselink et al. [6] were the first to document reduced quadriceps muscle strength, as assessed by isometric peak torque (PT), in patients with COPD, showing it to be a predictor of reduced maximum oxygen uptake (VO_2). In addition, patients with COPD have decreased

✉ Ernesto Cesar Pinto Leal-Junior
ernesto.leal.junior@gmail.com

1 Postgraduate Program in Rehabilitation Sciences, Nove de Julho University, São Paulo, SP, Brazil

2 Laboratory of Phototherapy and Innovative Technologies in Health, Nove de Julho University, 01504-001, Rua Vergueiro 235, Sao Paulo, SP, Brasil

muscle endurance when compared with healthy individuals. A plausible explanation for this reduction is abnormal muscle metabolism in which oxidative activity is lower [7].

Different functional tests are commonly used to evaluate exercise tolerance in this population due to the limiting factor of both muscle fatigue and dyspnea. The 6-minute walk test (6MWT) is sensitive and reproducible and is commonly used to evaluate the course of exercise tolerance in the context of out/inpatient pulmonary rehabilitation (PR) with a well-defined minimum clinically important difference [8–11]. According to the American Thoracic Society (ATS) guidelines [12], the 6MWT must be performed in an unobstructed 30-m hallway, but such a space is rarely available in the patient's home [13] or in the physician's office, or even in some respiratory medicine departments. The 6-minute stepper test (6MST) has several advantages when compared with other tests of functional capacity. This test requires only a limited amount of space and equipment and is feasible, easy to perform, sensitive, well tolerated, and reproducible in COPD patients [14, 15]. The 6MST has been used to assess exercise tolerance in the context of PR [16, 17]. However, the correlation between the 6MST and validated indices used to measure exercise capacity (6MWT and cardiopulmonary exercise testing) has not yet been established.

Several electrophysical interventions are being studied to minimize or delay muscle fatigue. In many studies, photobiomodulation therapy (PBMT) has been used as a non-invasive therapeutic modality to increase muscle vasodilation, improve collateral circulation, increase the level of oxygen in the tissue, and increase mitochondrial adenosine triphosphate (ATP) in peripheral muscles in different diseases [18–20]. On the other hand, static magnetic fields are able to decrease oxidative stress, increase antioxidant activity [21], and also increase mitochondrial adenosine triphosphate (ATP) production [22]. Moreover, the combination of PBMT (super-pulsed infrared laser, red LED, and infrared LED) and static magnetic field demonstrated remarkable synergy, leading to enhanced electron transfer and consequent activation of mitochondrial respiratory chain and ATP production [23].

The mechanisms involved in muscle performance improvement with the use of PBMT are not completely understood. It has been speculated that improvement may be due to minimization of oxidative stress [24], increase in local blood flow [18], and accelerated lactate removal [25]. Few human studies have evaluated the effects of PBMT on peripheral muscle function, but the results converge to positive effects on muscle performance.

A previous study by Miranda et al. [26] was the first to study the effects of PBMT in patients with COPD. The authors found a smaller decrease in the median frequency (electromyographic outcome for the evaluation of muscle fatigue) after an isometric endurance test and an increase in the muscle endurance test in 10 patients with COPD (VEF_1 50 ± 13% of predicted) after the application of PBMT to the quadriceps muscle.

Based on previous studies, we believe that the use of PBMT may improve the performance of patients with COPD during 6MST by minimizing muscle fatigue and increasing exercise tolerance through its therapeutic effect on vasodilation, improvement in collateral circulation, increases in the level of oxygen content in the tissues, and increase in the mitochondrial level of ATP [18, 27].

Therefore, the aim of this study was to evaluate the acute effect of PBMT with combined use of lasers, LEDs, and magnetic field on muscle performance, exercise tolerance, and metabolic variables during the 6MST in patients with COPD.

Methods

Study design

We performed a crossover, randomized, and triple-blind (assessors, therapists, and patients) clinical trial. The study was conducted in the Laboratory of Phototherapy and Innovative Technologies in Health.

Ethical aspects

All patients signed an informed consent form prior to enrollment, and the study was approved by the research ethics committee of Nove de Julho University (process 2100805) and the clinical trial was registered (NCT03639220).

Sample

The sample size ($n = 21$) was calculated assuming a type I error of 0.05 and a type II error of 0.2, based on previous study [28]. Patients were consecutively recruited from the outpatient chronic pulmonary diseases clinic at the Nove de Julho University. All patients had a diagnosis of COPD according to the global initiative for chronic obstructive lung disease (GOLD) criteria [1]. The patients were at a stable phase of the disease, indicated by a lack of change in medical therapy (including oral steroids) or an exacerbation of symptoms in the preceding 4 weeks. Patients with other known severe chronic diseases, including cardiac, neuromuscular, or orthopedic disorders, were excluded.

Randomization and blinding procedures

The order of treatments was randomized. We generated codes through a (random.org) website to ensure that 50% of our participants received the active treatment at session 1 and 50% received the active treatment at session 2, in order to counterbalance participants between the treatments tested (active and placebo) during the two sessions.

Randomization was performed to determine whether the active combination of super-pulsed lasers, LEDs, and magnetic field comprising the PBMT/magnetic field or the placebo would be given during the first session. During the second session, participants received the opposite treatment compared to their first session. Randomization labels were created according the randomization procedure through the (random.org) website, and a series of sealed, opaque, and numbered envelopes were created to ensure confidentiality. A participating researcher who programmed the PBMT/magnetic field device (Multi Radiance Medical™, Solon, OH) based on the randomization results performed the randomization. He was instructed not to inform the participants or other researchers of the PBMT/magnetic field dose (active or placebo). Thus, the researcher who performed the PBMT/magnetic field was blinded to the dose administered to the participants. To further maintain blinding, participants used opaque goggles to prevent them from seeing whether a light was being irradiated.

Protocol

Patients were administered either PBMT/magnetic field or placebo treatments during two visits, 1 week apart. The patients had been assessed for the 6MST performance (absolute and relative $VO_{2\ max}$, maximum heart rate, and time to exhaustion). A summary of the protocol is presented in Fig. 1.

Procedures

Spirometry Spirometry (CPFS/D USB, Medical Graphics, St. Paul, Minnesota) was conducted as per American Thoracic Society/European Respiratory Society criteria [29], FVC, FEV_1, and FEV_1/FVC are expressed in absolute values and percent of predicted [30].

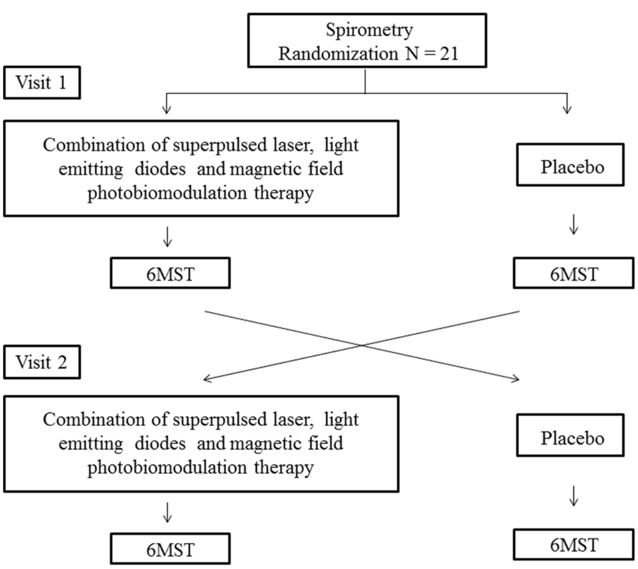


Fig. 1 Flowchart of study procedures

Photobiomodulation therapy and magnetic field Active PBMT/magnetic field combining super-pulsed lasers, LEDs, and magnetic field or a placebo was administered immediately before the 6MST (3–5 min). PBMT was applied employing MR4 Laser Therapy System outfitted with LaserShower 50 4-D emitters (both manufactured by Multi Radiance Medical™, Solon, OH, USA). We used a 12-diode cluster of super-pulsed lasers, LEDs, and magnetic field. Each cluster consisted of 4 diodes of 905-nm super-pulsed laser with an average power of 0.3125 mW and a peak power of 12.5 W for each diode, 4 diodes of 875-nm infrared LEDs with an average power of 17.5 mW for each diode, 4 diodes of 640-nm red LEDs with an average power of 15 mW for each diode, and a magnetic field of 35 mT. Given the large area of irradiation, the use of clusters was fundamental to the application of the therapy. We applied the PBMT with the cluster in direct contact with the skin at 9 sites on the knee extensor muscles (Fig. 2a), 6 sites on the knee flexors, and 2 sites on the calf (Fig. 2b) [28, 31]. The same procedures were performed to administer the placebo but without effective irradiation.

We chose the PBMT/magnetic field parameters based on previous studies [32, 33] using the same device. A full description of the PBMT/magnetic field parameters is provided in Table 1. The sounds emitted by the device were identical regardless of whether irradiation was present. A single researcher without knowledge of the randomization performed PBMT/magnetic field.

Six-minute stepper test A blinded researcher was in charge to carry out the 6MST. The 6MST aims to measure the number of steps performed on a stepper in 6 min using a protocol, that is, equivalent to the 6MWT protocol [34]. A step was defined

Fig. 2 **a** Treatment points in knee extensor muscles. **b** Treatment points in knee flexor and ankle plantar flexor muscles

Table 1 PBMT/magnetic field parameters

Number of lasers	4 super-pulsed infrared
Wavelength (nm)	905 (± 1)
Frequency (Hz)	250
Peak power (W), each	12.5
Average mean optical output (mW), each	0.3125
Power density (mW/cm^2), each	0.71
Energy density (J/cm^2), each	0.162
Dose (J), each	0.07125
Spot size of laser (cm^2), each	0.44
Number of red LEDs	4 red
Wavelength of red LEDs (nm)	640 (± 10)
Frequency (Hz)	2
Average optical output (mW), each	15
Power density (mW/cm^2), each	16.66
Energy density (J/cm^2), each	3.8
Dose (J), each	3.42
Spot size of red LED (cm^2), each	0.9
Number of infrared LEDs	4 infrared
Wavelength of infrared LEDs (nm)	875 (± 10)
Frequency (Hz)	16
Average optical output (mW), each	17.5
Power density (mW/cm^2), each	19.44
Energy density (J/cm^2), each	4.43
Dose (J), each	3.99
Spot size of LED (cm^2), each	0.9
Number of magnets	1
Shape	Ring
Area (cm^2)	20
Width (cm)	0.5
Thick (cm)	2
Magnetic field (mT)	35
Irradiation time per site (sec)	228
Total dose per site (J)	30
Total dose applied per lower limb (J)	510
Aperture of device (cm^2)	20
Application mode	Cluster probe held stationary in skin contact with a 90° angle and slight pressure

as a single complete movement of raising one foot and putting it down. The stepper (Carci®, São Paulo, SP, Brazil) was placed on the ground facing a wall to allow patients to maintain their balance by placing their fingers on the wall. The step height was set at 20 cm. Patients received standardized instructions adapted from the 6MWT ATS instructions [35] advising them to take the most number of steps they could in 6 min. The number of steps performed in 6 min was recorded. Monitoring of heart rate and SpO_2 by a pulse oximeter (Oxymontre 3100; Nonin) was performed each minute. A researcher was behind the patient throughout the test for safety.

During the 6MST, the rates of oxygen consumption (VO_2) and the production of carbon dioxide (CO_2) were measured using a gas analyzer (VO2000, Inbrasport®, Brazil), number of steps and heart rate (measured using a digital electrocardiograph (Medical Graphs Ergomet®, Brazil) were also monitored.

These data were used in the evaluation of the performance of the subjects for the exercise protocol, and it is currently widely used in the literature for this purpose [36]. The entire test was accompanied by electrocardiogram and blood pressure measurements. If any abnormal change in heart rate, blood pressure, or a complaint by the participant occurred, the test was stopped and the participant data deleted.

Before and after the exercise protocol, the perceived exertion (dyspnea and fatigue in the lower limbs) was assessed using a modified Borg scale [37].

Statistical analysis

The intention-to-treat analysis was followed a priori. The researcher that performed statistical analysis was blinded to randomization and allocation of volunteers in experimental groups. The Shapiro-Wilk test was used to verify the normal distribution of data. Parametric data were expressed as means and standard deviations. Non-parametric data were expressed as medians and interquartile intervals. Differences in the Borg scale before and after exercise comparing PBMT/magnetic field and placebo were evaluated first using the Friedman and secondarily the Wilcoxon test.

We used paired, two-sided t tests to compare the variables of exercise capacity, cardiorespiratory responses to exercise, and muscular function variables between PBMT/magnetic field and placebo, $p < 0.05$ was considered indicative of statistical significance.

Results

Despite intention-to-treat analysis was followed a priori in this study, there were no dropouts. Baseline characteristics of the 21 patients (100% adherence to protocol, 10 female, 11 male) are shown in Table 2. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, most of the patients ($n = 14$) had severe obstruction, and the remaining patients ($n = 7$) had moderate obstruction.

Table 3 shows the main variables evaluated during the 6MST. The PBMT/magnetic field group had a statistically significant lower score for the perception of breathlessness (3.0 [1.0–7.0] vs 4.0 [2.0–8.0], $p = 0.000$) and lower limb

Table 2 Participants characteristics

Variable	Mean ± SD
Age, year	64.1 ± 9.9
FEV_1, L (% predicted)	1.11 ± 0.3 (46.3 ± 10.5)
FVC_1, L (% predicted)	2.23 ± 0.8 (66.0 ± 14.7)
FEV_1/FCV, %	59.8 ± 12.3
Body mass index[a]	26.5 ± 5.9
Heart rate, beats per minute	80.3 ± 16.3
Systolic blood pressure, mmHg	117.5 ± 9.2
Diastolic blood pressure, mmHg	94.9 ± 3.6
Oxygen saturation, %	94.9 ± 3.6
Borg scale score—dyspnea	0.5 (0.0–4.0)
Borg scale score—lower limb fatigue	0.0 (0.0–2.0)

[a] Calculated as Kg/m^2. Values are in mean and standard deviation and median

fatigue (2.0 [0.0–5.0] vs 4.0 [0.0–7.0], $p = 0.001$) respectively compared with the placebo group.

The number of steps during the 6MST was greater with the application of PBMT/magnetic field prior to the test (129.8 ± 10.6) compared with that using placebo (116.1 ± 11.5, p = 0.000; Fig. 3).

Discussion

To our knowledge, this study is the first to assess the applicability of PBMT/magnetic field, using a combination of super-pulsed lasers, LEDs, and magnetic field, prior to a functional capacity test (6MST) in patients with COPD. The main finding of this study was that, the greatest number of climbs and descents during the 6MST, as well as the lowest perceived exertion for both dyspnea and lower limb fatigue using the modified Borg scale, occurred when PBMT was performed prior to the 6MST.

Peripheral muscle dysfunction in patients with COPD is characterized by macro- and microstructural changes in the peripheral muscles. From a macrostructural point of view, there is a reduction of muscle strength and endurance, as well as a reduction of muscle mass. The microstructural changes are characterized by the redistribution of the types of fibers (a reduction in the proportion of oxidative fibers and an increase in the proportion of glycolytic fibers), change in bioenergetics (attenuation of mitochondrial enzyme activity), and decapillarization (loss of capillary density) [38, 39]. Therefore, the use of PBMT in the rehabilitation of these patients is biologically supported.

PBMT is a promising and non-invasive procedure, that is, currently in wide use for reversal of muscle fatigue and recovery from musculoskeletal injuries [40]. A recent systematic review with meta-analysis [41] found positive results using a combination of lasers and LEDs, with a wavelength range of 655 to 950 nm, and an energy dose of 20 to 60 J for small muscle groups, and 60 to 300 J for large muscle groups. This review established a window for the parameters of PBMT for young and healthy individuals for the very first time. As no PBMT parameters have been established for diseases, the results of the present study can be used to corroborate this therapeutic window [41]. In addition, several studies have shown beneficial effects of PBMT, the removal of blood lactate [42], decrease in inflammatory processes [24, 25], stimulation of arteriolar vasodilation, and improvement of peripheral microcirculation [18, 27], with consequent increases in muscle oxygen supply and mitochondrial ATP [19].

Table 3 Data at the peak of exercise

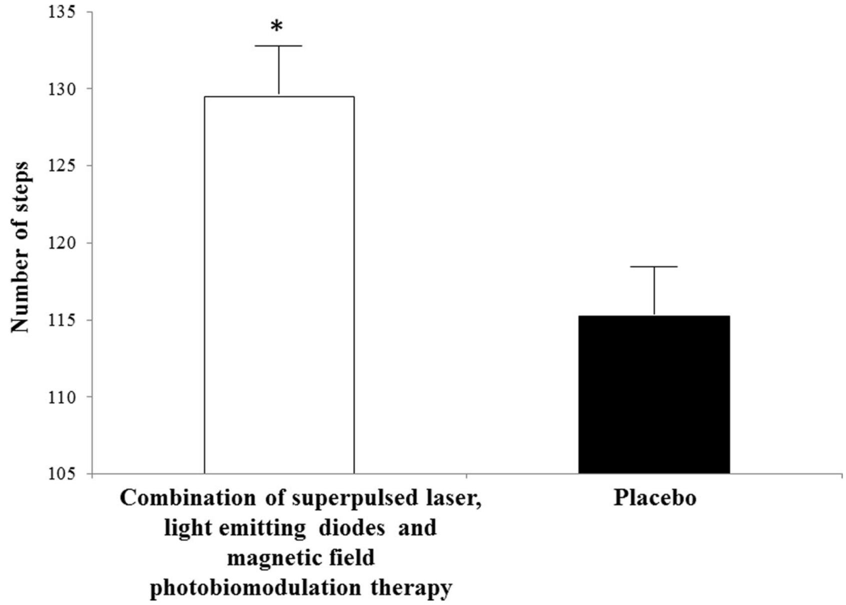
Variable	Treatment		95% CI
	Placebo	Combination of super-pulsed laser, light-emitting diodes, and photobiomodulation therapy	
Metabolic rate (mean ± SD)			
VO_2 (mL/kg/min)	8.8 ± 1.6	12.2 ± 2.9	− 2.34, 9.06
VCO_2 (mL/kg/min)	10.9 ± 2.7	13.7 ± 1.5	− 2.70, 8.33
VE (L/min)	26.5 ± 9.2	29.8 ± 7.3	− 10.08, 16.63
Borg scale score, median (interquartile range)			
Dyspnea	4.0 (2.0–8.0)	3.0 (1.0–7.0)*	2.75, 4.85
Lower limb fatigue	4.0 (0.0–7.0)	2.0 (0.0–5.0)*	1.85, 3.97
6MST, number of steps	116.1 ± 11.5	129.8 ± 10.6*	7.37, 20.19

Data is expressed in average and standard deviation (±)

VO_2, oxygen uptake; *VCO_2*, carbon dioxide production; *VE*, pulmonary ventilation; *6MST*, 6-minute stepper test

*Statistically significant difference between groups ($p < 0.05$)

Fig. 3 Number of steps performed



A previous study using PBMT/magnetic field to improve muscle performance in 13 patients with COPD observed that the combination of lasers, LEDs, and magnetic field could increase the peak torque by 20.2% and the total work by 12%, when evaluated with an isokinetic dynamometer [33]. We observed in our study an increase of approximately 10.6% in the number of steps after a single application of PBMT/magnetic field in 21 patients with COPD. Despite the beneficial effect of PBMT/magnetic field, we believe that the 6MST is more fatiguing for COPD patients, due to the use of several lower limb muscle groups and greater time required for the test, when compared with a strength test using an isokinetic dynamometer.

Furthermore, a significant increase in the number of steps on the 6MST (from 488 to 570) was observed not only after outpatient PR [15], but also after home PR in a population of patients with idiopathic pulmonary fibrosis [43], unselected patients with more severe chronic lung disease (80% on the long-term oxygen therapy and/or non-invasive ventilation), and COPD patients [16, 17]. This is the first study to evaluate the effect of PBMT in patients with COPD during the 6MST. When evaluating the 6MST after a long period of PR, the authors found an average increase of 82 steps. Our study observed an increase of 13 steps after a single application of PBMT/magnetic field. Therefore, we believe that the use of PBMT/magnetic field effectively increases performance during exercise in this population when applied acutely.

Pinto et al. [44] evaluated the effects of PBMT/magnetic field with the combination of lasers, LEDs, and magnetic field on performance and recovery in 12 rugby athletes during an anaerobic field test (Bangsbo Sprint test, BST) and observed a decrease in both blood lactate levels and perceived exertion. Despite differences in the population studied and tests employed, both the report by Pinto et al. [44] and the present study found positive results with the use of PBMT/magnetic field comprising the combination of lasers, LEDs, and magnetic field prior to exercises. Regardless of the patients studied, the physiological effects [28, 32, 33, 44] of PBMT/magnetic field (with the combination of lasers, LEDs, and magnetic field) are effective in enhancing performance during functional testing.

Corroborating our findings, the combination of superpulsed lasers, LEDs, and magnetic field when compared to placebo was also able to decrease the dyspnea score (3.0 [0.5–9.0] vs 4.0 [0.0–9.0], $p = 0.001$) in 20 healthy participants during a treadmill cardiopulmonary test [28] in a previous study. The present study found a significant decrease in the dyspnea score in patients with COPD (4.0 [2.0–8.0] vs 3.0 [1.0–7.0], $p = 0.000$), corroborating with previous findings where the combination of super-pulsed lasers, LEDs, and magnetic was used.

Miranda et al. [26] also observed a reduced dyspnea score in 10 patients with COPD during a single application of PBMT (combination of red and infrared LEDs) prior to an isometric endurance exercise test, the dyspnea score for endurance time was lower with PBMT in comparison with placebo (0.3 ± 0.2 vs. 0.8 ± 0.4 respectively, $p = 0.008$). Our results are in agreement with previous studies showing a decrease in the dyspnea score in patients with COPD (4.0 [2.0–8.0] vs 3.0 [1.0–7.0], $p = 0.000$); therefore, we believe that a lower score on the dyspnea score after application of PBMT can be a good indicator of improvement in the physical capacity of individuals with COPD.

Modulation in mitochondrial activity is a key mechanism in PBMT [45, 46]. A recent experimental study showed that the use of PBMT with different wavelengths (660, 830, and 905 nm) and doses (1 and 3 J) increased the expression of cytochrome c oxidase in different time windows ranging from 5 min to 24 h after PBMT irradiation [47]. This factor contributes to the understanding of how PBMT can improve performance and protect muscles against the development of fatigue and tissue damage [48].

The beneficial effects of PBMT/magnetic field with the combination of super-pulsed lasers, LEDs, and magnetic field have been described recently in the literature [28, 32, 33, 44]. Researchers have shown that a combination of different light sources and magnetic field enhances muscular performance [32, 33], decreases pain [49, 50], decreases fatigue development [32, 51], and protects muscles against gradually worsening damage [32, 51].

Regarding mechanisms, recently, Albuquerque-Pontes et al. [47] showed that PBMT with different wavelengths (660, 830, or 905 nm) was able to increase the expression of cytochrome c oxidase in the intact skeletal muscle tissue in different time windows (5 min to 24 h after irradiation), which means that the muscle metabolism can be improved through the action of PBMT. These findings help us to explain the increase in performance observed by the use of pre-exercise PBMT observed in the current study and provide the rationale for the concurrent use of different wavelengths at the same time, which can represent a therapeutic advantage in various clinical situations.

Our findings do not elucidate if the contention of a magnetic field in the cluster device is a differential component for performance enhancement. Moreover, it was not possible to have any perception regarding the action of the magnetic field in this study. However, a previous study showed that the combination of PBMT (super-pulsed infrared laser, red LED, and infrared LED) and static magnetic field demonstrated remarkable synergy, leading to enhanced electron transfer and consequent activation of mitochondrial respiratory chain and ATP production [23]. Thus, the impact of the inclusion of magnetic field in the composition of this device should be a prominent topic for further clinical investigation.

Conclusion

This study showed that the combination of PBMT and magnetic field increased the number of steps during the 6MST and decreased the sensation of dyspnea and lower limb fatigue in patients with COPD.

Funding This study was supported by research grants 2010/52404-0 from São Paulo Research Foundation, FAPESP (Professor Ernesto Cesar Pinto Leal-Junior), 310281/2017-2 from Brazilian Council of Science and Technology Development, CNPq (Professor Ernesto Cesar Pinto Leal-Junior). FAPESP and CNPq had no role in the planning of this study; they had no influence on study design, data collection and analysis, decision to publish, or preparation of the article.

Compliance with ethical standards

Competing interests Professor Ernesto Cesar Pinto Leal-Junior receives research support from Multi-Radiance Medical (Solon, OH, USA), a phototherapy/photobiomodulation device manufacturer. The remaining authors declare that they have no conflict of interests.

Ethical approval All experimental procedures were submitted and approved by the Research Ethics Committee of Nove de Julho University (process number 2100805) and registered at Clinical Trials.gov (NCT03639220).

Statement of informed consent All patients signed an informed consent form prior to enrollment.

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