Safety and Feasibility of a Multimodal Physiotherapeutic Care Protocol with Vascular Photobiomodulation in Women with Breast Cancer: Randomized Pilot Study

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Segurança e Viabilidade de Protocolo Fisioterapêutico Multimodal de Cuidado com Fotobiomodulação Vascular em Mulheres com Câncer de Mama: Estudo-Piloto Randomizado

Seguridad y Viabilidad de Protocolo Fisioterapéutico Multimodal de Cuidado con Fotobiomodulación Vascular en Mujeres con Cáncer de Mama: Estudio Piloto Aleatorizado

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ABSTRACT

Introduction: Breast cancer and its antineoplastic treatment are associated with physical and functional adverse events, requiring safe supportive care strategies. Multimodal physiotherapy protocols have been used for this purpose, and vascular photobiomodulation (VPBM) has emerged as a potentially adjunctive resource. **Objective:** To evaluate the clinical safety, feasibility, and acceptability of a multimodal physiotherapy protocol including VPBM, compared with a placebo application. **Method:** This pilot randomized, double-blind, placebo-controlled clinical trial with a parallel design allocated participants to either an intervention or placebo group. Participants underwent ten sessions over five weeks, including transdermal application of VPBM over the left radial artery. Outcomes included patient-reported adverse events, tolerability, adherence, and satisfaction. Pain, heaviness sensation, and perceived edema were assessed as exploratory secondary outcomes. **Results:** Twelve women initiated the protocol, with 100% adherence. No serious adverse events were observed. Across 120 applications, eight episodes of mild, transient, and self-limited discomfort were reported, more frequently in the intervention group, without requiring interruption. An intragroup reduction in the musculoskeletal pain domain was observed (p=0.035), with no differences between groups; this finding was interpreted as exploratory. Acceptability was high, with elevated satisfaction levels in both groups. **Conclusion:** The multimodal physiotherapy protocol including VPBM was feasible, well tolerated, and well accepted in women undergoing treatment for breast cancer. Due to the pilot nature and multimodal design, no specific effects can be attributed to VPBM, reinforcing the need for confirmatory studies.

Key words: Breast Neoplasms; Physical Therapy Modalities; Low-Level Light Therapy/adverse effects.

RESUMO

Introdução: O câncer de mama e seu tratamento antineoplásico estão associados a eventos adversos físicos e funcionais, demandando estratégias seguras de cuidado de suporte. Protocolos fisioterapêuticos multimodais têm sido utilizados com esse propósito e a fotobiomodulação vascular (FV) surge como recurso potencialmente adjuvante. **Objetivo:** Avaliar a segurança clínica, a viabilidade e a aceitabilidade de um protocolo fisioterapêutico multimodal com FV, comparado ao placebo. **Método:** Estudo clínico-piloto, randomizado, duplo-cego, placebo-controlado, com delineamento paralelo. As participantes foram alocadas em grupo intervenção ou placebo e submetidas a dez sessões, ao longo de cinco semanas, com aplicação transdérmica da FV sobre a artéria radial esquerda. Os desfechos incluíram eventos adversos autorreferidos, tolerabilidade, adesão e satisfação. Dor, sensação de peso e percepção de edema foram avaliados como desfechos secundários exploratórios. **Resultados:** Doze mulheres iniciaram o protocolo, com adesão de 100%. Não foram observados eventos adversos graves. Ao longo de 120 aplicações, foram registrados oito episódios de desconforto leve, transitório e autolimitado, com mais frequência no grupo intervenção, sem necessidade de interrupção. Observou-se redução intragrupo no domínio dor/musculoesquelética (*p*=0,035), sem diferenças entre grupos, sendo esse achado interpretado de forma exploratória. A aceitabilidade foi elevada, com altos níveis de satisfação em ambos os grupos. **Conclusão:** O protocolo fisioterapêutico multimodal com FV mostrou-se viável, tolerável e bem aceito em mulheres com câncer de mama em tratamento antineoplásico. Em razão da natureza piloto e do delineamento multimodal, não é possível atribuir efeitos específicos à FV, reforçando a necessidade de estudos confirmatórios.

Palavras-chave: Neoplasias da Mama; Modalidades de Fisioterapia; Terapia com Luz de Baixa Intensidade/efeitos adversos.

RESUMEN

Introducción: El cáncer de mama y su tratamiento antineoplásico se asocian con eventos adversos físicos y funcionales, lo que demanda estrategias seguras de cuidado de soporte. Los protocolos fisioterapéuticos multimodales han sido utilizados con este propósito, y la fotobiomodulación vascular (FV) surge como un recurso potencialmente adyuvante. **Objetivo:** Evaluar la seguridad clínica, la viabilidad y la aceptabilidad de un protocolo fisioterapéutico multimodal que incluye FV, en comparación con una aplicación placebo. **Método:** Estudio clínico piloto, aleatorizado, doble ciego, controlado con placebo, con diseño paralelo. Las participantes fueron asignadas a un grupo de intervención o placebo y sometidas a diez sesiones a lo largo de cinco semanas, incluyendo la aplicación transdérmica de FV sobre la arteria radial izquierda. Los desenlaces incluyeron eventos adversos autorreportados, tolerancia, compromiso y satisfacción. El dolor, la sensación de pesadez y la percepción de edema fueron evaluados como desenlaces secundarios exploratorios. **Resultados:** Doce mujeres iniciaron el protocolo, con una tasa de compromiso del 100%. No se observaron eventos adversos graves. A lo largo de 120 aplicaciones, se registraron ocho episodios de molestias leves, transitorias y autolimitadas, más frecuentes en el grupo de intervención, sin necesidad de interrupción. Se observó una reducción intragrupo en el dominio de dolor musculoesquelético (p=0,035), sin diferencias entre los grupos; este hallazgo fue interpretado como exploratorio. La aceptabilidad fue elevada, con altos niveles de satisfacción en ambos grupos. **Conclusión:** El protocolo fisioterapéutico multimodal con FV mostró ser viable, bien tolerado así como bien aceptado en mujeres en tratamiento antineoplásico con cáncer de mama. Debido a la naturaleza piloto y al diseño multimodal, no es posible atribuir efectos específicos a la FV, lo que refuerza la necesidad de estudios confirmatorios.

Palabras clave: Neoplasias de la Mama; Modalidades de Fisioterapia; Terapia por Luz de Baja Intensidad/efectos adversos.

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INTRODUCTION

Breast cancer is the most common neoplasm among women in Brazil and a serious public health issue. In Brazil, approximately 78,610 new breast cancer cases are estimated per year for the 2026-2028 triennium, corresponding to an incidence rate of about 71.57 cases per 100 thousand women[1]. Disregarding non-melanoma skin tumors, female breast cancer remains the most common neoplasm in the country, reinforcing the magnitude of the oncological burden and its impacts on morbidity, mortality, and quality of life[1].

Despite an increase in survival, antineoplastic treatment is associated with physical, functional, and psychosocial adverse effects that compromise the experience of care during and after treatment[2]. Among the adverse effects most commonly reported by women with breast cancer in antineoplastic treatment, musculoskeletal pain, heaviness sensation, perceived edema of the upper limbs, skin alterations, fatigue, sleeping disorders, emotional symptoms, and harms to body image stand out[3,4]. These symptoms interfere negatively with functionality, therapeutic adherence, and social and occupational reintegration of patients[5].

To capture these events in a standardized way, instruments based on self-reported outcomes have broadened the understanding of the subjective experience of treatment, enabling the documentation of symptoms and adverse events that are not always adequately identified by clinical assessments. The Patient-Reported Outcomes version for the Common Terminology Criteria for Adverse Events (PRO-CTCAE)[6-8] was developed for that purpose and has been widely used to measure, in a standardized and validated way, the direct frequency, intensity, and functional impact of adverse events on patients.

Given the complexity and multifactorial nature of symptoms associated with cancer and its treatment, supportive care models based on multimodal and integrated approaches have been progressively incorporated into oncological practice, with emphasis on patient-centered strategies and interdisciplinary action[9]. These approaches acknowledge that isolated interventions are not always enough to address the diversity of physical, functional, and psychosocial demands; therefore, the combination of different non-pharmacological strategies, individually and safely implemented, is recommended[9,10]. In the scope of oncological physiotherapy, multimodal interventions that integrate therapeutic resources, well-being strategies, and education have demonstrated the potential to improve the experience of care, favoring adherence to treatment and contributing to symptom management, as long as they are viable and well-accepted by patients[10].

Vascular photobiomodulation (VPBM) is a specific modality of low-intensity laser therapy application on blood vessels to modulate systemic biological processes through light interaction with blood components and the vascular wall[11]. Traditionally, this technique has been described as intravascular laser irradiation of blood (ILIB), conducted through an invasive route, using an optical fiber attached to an intravenous catheter. However, this approach presents relevant limitations in the clinical context, such as its invasiveness, discomfort, and lower patient acceptability.

As an alternative, non-invasive approaches have been developed, based on transdermal or transmucosal application of light to peripheral vessels, using devices such as bracelets. In this context, the use of ILIB-derived terms, such as modified intravascular laser irradiation of blood (mILIB), has been considered potentially ambiguous. It is therefore recommended to adopt the vascular photobiomodulation terminology to describe these non-invasive approaches, as it more precisely represents the array of techniques and application sites, avoiding mistaken interpretations regarding the intravascular character of the intervention[11,12].

From a physiological point of view, photobiomodulation has been associated with the modulation of inflammatory processes, influence on microcirculation, and activation of cellular mechanisms related to analgesia, immunomodulation, and tissue homeostasis[13,14]. Evidence from experimental, initial clinical, and integrative review studies suggests that photobiomodulation can have analgesic and anti-inflammatory effects, in addition to acting as adjuvant therapy in different chronic systemic conditions[13-15]. In the context of VPBM, preliminary observations indicate potential benefits in attenuating adverse effects related to antineoplastic treatment, including inflammatory complications and hematopoietic alterations[16,17].

A relevant characteristic of transdermal VPBM is the possibility of applying it along with other therapeutic interventions, since the device can be used continuously during the execution of different techniques, without interference. In this sense, VPBM can be integrated into multimodal physiotherapeutic protocols that include resources such as kinesiotherapy, manual therapies, educational strategies, and integrative practices. Integrative and multimodal approaches have been progressively incorporated into oncological care, with emphasis on patient-centered strategies and interdisciplinary work[18,19].

Despite these promising findings, clinical studies involving VPBM are still limited, heterogeneous, and mostly conducted with different dosimetry protocols and distinct clinical populations[11,12]. In women with breast

cancer, particularly, there are still relevant gaps regarding systematic assessment of clinical safety, tolerability, and viability of VPBM when applied as part of a multimodal physiotherapeutic supportive care protocol, justifying the conduction of pilot studies with this focus.

As this is a pilot clinical trial, the present study was designed to assess essential aspects before the conduct of confirmatory studies, including the occurrence of adverse events, acceptability of the intervention, adherence of participants, and viability of protocol implementation in the clinical context, as previously described in their published protocol[20]. In the oncology field, this step is particularly relevant, since new supportive care strategies must, as a priority, demonstrate safety and compatibility with conventional antineoplastic treatment, in addition to being viable in the care routine.

Therefore, the general objective of the present study was to assess the clinical safety, viability, and acceptability of a multimodal physiotherapeutic supportive care protocol, including VPBM as one of its components, compared to a placebo application group, in women with primary breast cancer in antineoplastic treatment, considering the occurrence of self-reported adverse events, tolerability of the intervention, protocol adherence rate, satisfaction of participants, and preliminary exploration of secondary clinical outcomes.

METHOD

Pilot randomized, double-blind, placebo-controlled clinical trial with a parallel design, in which all participants received a multimodal physiotherapeutic supportive care protocol, differing only regarding the application of active or placebo VPBM.

The study included women aged 21-75 years, with a clinical diagnosis of primary breast cancer, unilateral or bilateral, in adjuvant antineoplastic treatment (chemotherapy, radiotherapy, hormonal therapy, or immunotherapy), with a score between 0 and 2 in the Eastern Cooperative Oncology Group Performance Status (ECOG-PS)[21], verbal communication ability in Portuguese, and agreement to participate in the study.

The study excluded women with cognitive deficit assessed by the Mini-Mental State Examination below the cutoff points established for their age; hearing impairment that impaired their understanding of instructions; presence or suspicion of active metastatic disease; pregnant or lactating; body mass index above 40 kg/m²; clinical contraindications to VPBM[22] — including severe cardiopathies, coagulopathies, advanced circulatory insufficiency, arterial hypotension, sinus node dysfunction, cardiogenic shock, important anemia or presence of implantable devices; history of active cancer in addition to breast cancer, hemorrhagic or infected areas in the application site; and photosensitive skin (Photoype V) confirmed by phototype analyzer (*SkinUP*®).

The exclusion of participants with a skin phototype V was adopted considering possible variations in the light interaction with biological tissues, especially related to a greater concentration of melanin, which can influence light absorption and interpretation, as described in the literature about optical skin properties[23].

Assessments and interventions were conducted in the Center for Studies in Physiotherapy and Advanced Technological Innovation (Cefita), linked to the Department of Prevention and Rehabilitation in Physiotherapy of the Federal University of Paraná (UFPR), Curitiba, Brazil. Recruitment occurred by non-probabilistic convenience sampling, upon advertising the study in services linked to the university, in institutions that support women with breast cancer, and institutional social media profiles. Those who were interested reached out spontaneously to the research team, where they were initially screened remotely and later assessed in person to confirm the eligibility criteria and characterization of the sample.

After this initial assessment, the eligible participants were randomized into two groups: Intervention Group – GI (multimodal physiotherapeutic protocol associated with active VPBM) and Placebo Group – GP (same multimodal physiotherapeutic protocol associated with placebo VPBM). Randomization was conducted using an online sorting website, in blocks, ensuring an equivalent proportion between the groups. The study was double-blinded, in which participants and evaluators had no knowledge of the allocation. The distinction between active and placebo application was restricted to the researcher responsible for the intervention, not involved in the assessments.

The interventions occurred across 5 weeks, totaling 10 applications, with a frequency of 2 times a week and a duration of 30 minutes each.

VPBM was applied through a bracelet positioned on the left radial artery with the *Ecco* ILIB *Plus*® device (Figure 1). The continuous luminous beam is released by a single semiconductor red laser diode (660 nm-AlGaInP), with an emission area of 0.1 cm² and potency of 100 mW, emitted for 30 minutes, equal to the application of 180 J of energy and 1,800 J/cm² of energy density. In placebo, an identical device was used, with luminous emission with no therapeutic potency (red light-emitting diode, 1mW)[20].

Along with the VPBM application (active or placebo), all participants underwent a multimodal physiotherapeutic supportive care protocol previously

Figure 1. *Ecco* ILIB *Plus* equipment and its application in the left radial artery

published by the research group[20]. The protocol included clay therapy with a hydrating and revitalizing purpose for the facial skin, performed following sequential steps for skin cleansing, application of white clay, removal, and finalization with photoprotection, as described in the original protocol. Miofascial liberation protocols were conducted using pompage in the cervical (rotation and lateral inclination movements) and major pectoral regions, associated with respiratory exercises (diaphragmatic breathing, pursed-lip breathing, and *pranayama surya bedhana* technique). Additionally, mild kinesiotherapy was conducted, involving articular mobility exercises and stretching for the cervical region and shoulder complex. The participants also received general guidance on self-care, body perception, and promotion of well-being during the interventions. The possibility of simultaneous application is due to the transdermal nature of VPBM, enabling its integration with other physiotherapeutic approaches without technical or physiologic interference.

Considering the viability study design, the outcomes were organized into primary and secondary, according to the methodological recommendations for pilot trials. The primary outcomes were related to clinical safety, viability, and acceptability of the multimodal physiotherapeutic protocol and included: 1) Occurrence of self-reported adverse events, related to antineoplastic treatment and/or intervention, assessed by the Portuguese version, certified and authorized by the National Cancer Institute (NCI)[24], PRO-CTCAE; 2) Tolerability of the intervention, assessed by clinical observation during applications, associated with participants' self-reported discomfort and side effects. These pieces of information were immediately recorded after each application by the researcher in charge using an intervention follow-up sheet, with no structured real-time measurement during the application. The events were recorded regardless of its possible causal relation with the intervention; 3) Protocol adherence rate, defined as the proportion of participants who completed at least 75% of proposed sessions; 4) Participants' satisfaction, assessed through a structured questionnaire[25] applied at the end of the intervention protocol, composed of 10 questions with scores ranging from 1 (very dissatisfied) to 5 (very satisfied).

The outcomes were assessed at different points of the study. The clinical variables and exploratory secondary outcomes (pain, heaviness sensation, and perceived edema) were assessed at two time points: at the beginning of the study (baseline) and at the end of the intervention protocol, after completing ten sessions. Tolerability of the intervention was monitored across every session by clinical observation and participants' self-report, registered immediately after each application. The adverse events were assessed using the PRO-CTCAE, considering the look-back period of seven days before the assessment. No follow-up assessments were conducted after finishing the intervention.

It is noteworthy that PRO-CTCAE is a self-report instrument that assesses symptoms associated with oncological treatment, allowing participants to report the presence, frequency, severity, and interference in daily life activities of adverse events, considering the period of seven days before the intervention[6]. For toxicities with multiple attributes, scores range from 0 to 4, according to the NCI PRO-CTCAE Scoring Manual[6,7] guidelines, enabling measurement standardization and comparability between studies. Adverse events were organized in symptomatic domains, according to the algorithm proposed by the NCI[6,7] and validated in multicentric studies[26,27], resulting in 16 general domains with adequate conceptual coherence and clinical interpretability[28]. Of those, 10 domains were previously specified as primary outcomes of the present study, prioritizing clinically relevant adverse events, frequently reported by women with breast cancer and potentially modifiable by physiotherapeutic interventions, in line with contemporary methodological recommendations for the use of patient-reported outcomes in oncological clinical trials[29-31]. This strategy sought to increase analytical viability, clinical interpretation of the findings, and adherence to best methodological practices in a pilot trial.

Secondary outcomes were included with an exploratory character to provide preliminary information on the possible clinical effects of the protocol, without a confirmatory purpose. Pain, heaviness sensation, and perceived edema in the affected upper limb were assessed, measured by a numeric 11-point scale, in which higher values indicate greater symptom intensity.

Data was analyzed using the SPSS[32] software, version 21.0, following the principle of treatment intention, with absent data management due to the method of the last uploaded observation. Descriptive statistics were used to characterize the sample and outcomes. Considering the reduced sample size and the ordinal nature of outcomes, a non-parametric approach was adopted. Intragroup comparisons (pre- and post-) were conducted using the paired Wilcoxon test, and intergroup comparisons were assessed using the Mann-Whitney test, both described by Field[33]. The self-reported adverse events, assessed by the PRO-CTCAE[6-7], were analyzed in a descriptive and exploratory manner, with presentation of score distribution by domain and group. Tolerability, adherence, and satisfaction were described by frequencies, proportions, and central trend measures. The effect size was estimated by the *r* coefficient, categorized as small (<0.10), moderate (0.11 to 0.30), and large (>0.50), being interpreted descriptively. A significant level of $p<0.05$ was adopted, with careful interpretation of the findings, as recommended for pilot studies. Considering the pilot character of the study, inferential analyses were conducted with an exploratory purpose, with no confirmatory objective, and the results interpreted with caution and complemented by descriptive statistics.

The study was registered on the Brazilian Registry of Clinical Trials (ReBEC), number RBR-3cdtw97, approved by the Research Ethics Committee of the UFPR Health Sciences Department, report number 7167136 (CAAE: 71033323.9.0000.0102) and conducted in accordance with Resolutions from the National Health Council N. 466/2012 and N. 510/2016, which rule on studies conducted with human beings in Brazil[34,35]. The study also followed the Consolidated Standards of Reporting Trials (CONSORT) for pilot clinical trials and viability[36]. All the participants signed a Free and Informed Consent Form before their inclusion in the study.

RESULTS

A total of 24 women were randomized (Figure 2), of whom 12 effectively initiated the protocol (GI=6; GP=6). The main reason for not initiating the study was the prolonged interval between screening and the beginning of applications, with withdrawals before the first session. All the women who started the protocol completed the 10 expected interventions.

The sociodemographic and clinical characteristics of participants who initiated the study are presented in Table 1. Generally, the groups presented a similar distribution regarding the assessed variables, except for the practice of physical activity.

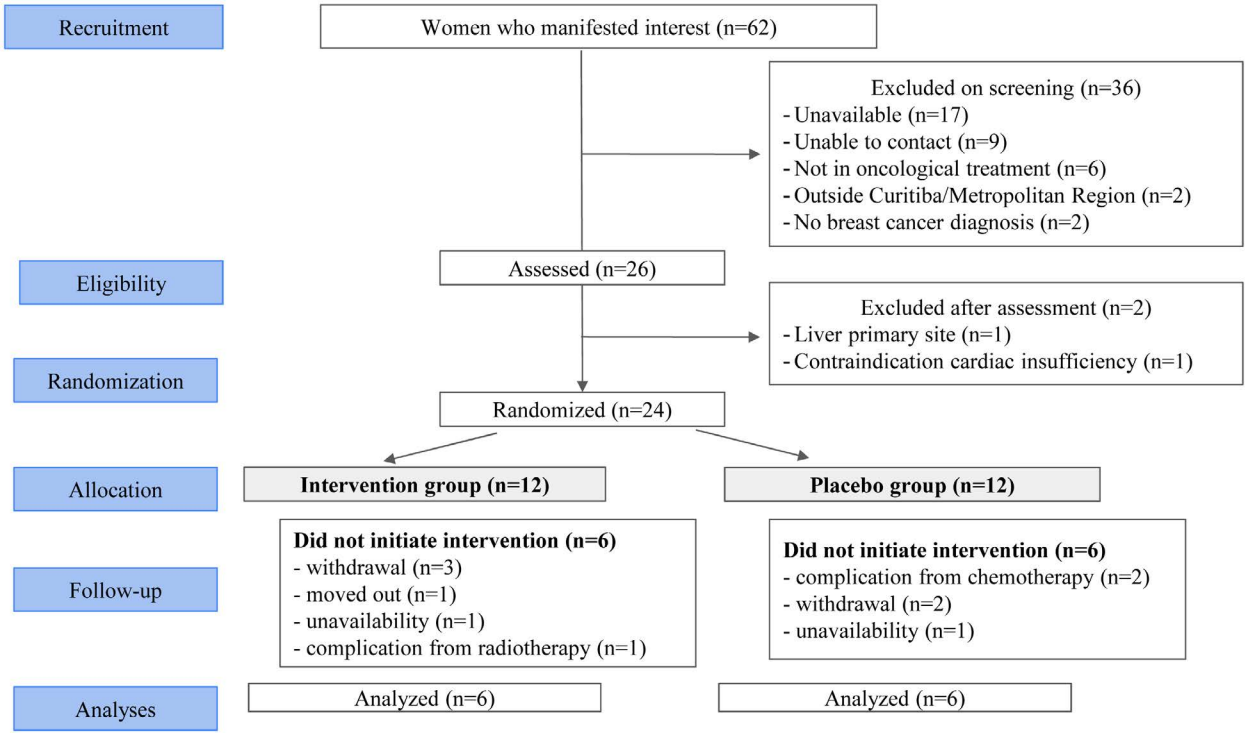

Figure 2. Descriptive flowchart of the study's phases according to CONSORT

Table 1. Sociodemographic characteristics of participants with breast cancer between the intervention and the placebo groups

Characteristics	GI (n=6)	GP (n=6)	*p*
Age (years) – mean(SD)	46.1 (14.7)	48.0 (6.1)	0.65
Place of residence			
Curitiba	4 (66.7)	5 (83.3)	0.37
Metropolitan Region	2 (33.3)	1 (16.7)	
Race – n (%)			
White	5 (83.3)	5 (83.3)	1.00
Brown	1 (16.7)	1 (16.7)	
Marital status – n (%)			
Single	1 (16.7)	0 (0.0)	0.49
Married	3 (50.0)	2 (33.3)	
Separated	0 (0.0)	1 (16.7)	
Divorced	2 (33.3)	3 (50.0)	
Education – n (%)			
Complete high school	1 (16.7)	0 (0.0)	0.54
Incomplete higher education	2 (33.3)	1 (16.7)	
Complete higher education	3 (50.0)	5 (83.3)	
Current occupation – n (%)			
Retired and/or pensioner	2 (33.3)	1 (16.7)	0.31
Works part time	1 (16.7)	0 (0.0)	
Works full time (> 30h/week)	2 (33.3)	5 (83.3)	
Medical leave	1 (16.7)	0 (0.0)	
Current occupation – n (%)			
Homemaker	2 (33.3)	1 (16.7)	0.30
Teaching position	2 (33.3)	0 (0.0)	
Pharmacist	1 (16.7)	0 (0.0)	
Lawyer	1 (16.7)	0 (0.0)	
Public worker	0 (0.0)	2 (33.3)	
Others	0 (0.0)	3 (50.1)	
Physical activity practice – n (%)			
Yes	5 (83.3)	0 (0.0)	0.03*
Functional condition (ECOG-OS) – n (%)			
0 – Fully active	2 (33.3)	3 (50.0)	0.55
1 – Restrictions regarding strenuous physical activities	2 (33.3)	3 (50.0)	
2 – Capable of performing all forms of self-care	2 (33;3)	0 (0.0)	
Site of primary tumor			
Left breast	3 (50.0)	1 (16.7)	0.54
Right breast	3 (50.0)	4 (66.7)	
Bilateral	0 (0.0)	1 (16.7)	
Emergence of tumor months - mean (SD)	29 (29.8)	46 (36.2)	0.32
Staging* (TNM) – n (%)			
T (primary tumor)			
Tis	0 (0.0)	2 (40.0)	0.39
T0	1 (20.0)	1 (20.0)	
T2	1 (20.0)	1 (20.0)	
T3	3 (60.0)	1 (20.0)	
N (regional lymph nodes)			
Nx	0 (0.0)	1 (20.0)	0.13
N0	1 (20.0)	3 (60.0)	
N1	3 (60.0)	0 (0.0)	
N2	0 (0.0)	1 (20.0)	
N3	1 (20.0)	0 (0.0)	
M (distant metastases)			
M0	5 (100.0)	5 (100.0)	1.00
M1	0 (0.0)	0 (0.0)	
Use of medication – n (%)			
Antidepressants	2 (33.3)	3 (50.0)	0.26
Antihypertensive	0 (0.0)	1 (16.7)	
Anxiolytic	0 (0.0)	1 (16.7)	
Other	4 (66.7)	1 (16.7)	
Current antineoplastic treatment - n (%)			
Chemotherapy	1 (16.7)	0 (0.0)	0.29
Radiotherapy	0 (0.0)	0 (0.0)	1.00
Hormone therapy	3 (50.0)	4 (66.7)	0.22
Immunotherapy	2 (33.3)	1 (16.7)	0.29
Hormone therapy + Immunotherapy	0 (0.0)	1 (16.7)	0.29

Captions: SD = standard deviation; * = Data available for 5 participants in each group. Percentages calculated based on valid data.

In PRO- CTCAE, an intragroup reduction in the musculoskeletal/pain domain was observed (p=0.035, r=0.32) in GI, with no differences between groups; this finding was interpreted as exploratory. In the other domains, no intra- or intergroup differences were observed (Table 2).

Regarding the tolerability of the intervention, across the protocol, 120 VPBM applications were done, 60 in GI and 60 in GP. Eight episodes of mild, transitory discomfort, self-limited, with no need to suspend the applications, were reported. These episodes were identified during sessions through clinical observation and participants' self-report, recorded immediately after each application. In GI, six episodes occurred, including nausea (n=3), cervical pain (n=2), and pain on the affected limb (n=1). In GP, two episodes of pain on the affected limb were identified. No cutaneous, cardiovascular, hematological, or systemic adverse events were observed during the intervention period. Considering the descriptive character and small number of events, no inferential analysis was done between groups.

Attendance at the sessions was high. Three participants attended all the scheduled sessions; six had one absence; two had two absences; and one participant had three absences during the intervention period. All absences

Table 2. Comparison of adverse events grouped by domains, at the different assessment times, between intervention and placebo groups

NCI PRO-CTCAE Domains	GI (n=6)	GP (n=6)	*GI T0 vs. T1 [95% CI], p*	*GP T0 vs. T1 [95% CI], p*
Gastrointestinal (0-4)			U=24.00; p=0.375; r=0.26	
Pre-intervention	0.55 (0.09-1.00)	0.27 (0.09-0.45)		
Post-intervention	0.82 (0.45-1.36)	0.45 (0.09-0.91)	[-0.64; 0.05], 0.093	**[-0.68; -0.27], 0.032***
Mucocutaneous/Oral (0-4)			U=23.50; p=0.414; r=0.24	
Pre-intervention	0.14 (0.00-0.86)	0.14 (0.00-1.00)		
Post-intervention	0.14 (0.00-0.43)	0.07 (0.00-0.29)	[-0.57; 0.36], 0.892	[-0.43; 0.00]; 0.166
Pain/Musculoskeletal (0-4)			U=16.50; p=0.870; r=0.05	
Pre-intervention	1.50 (0.50-4.00)	2.12 (0.25-2.50)		
Post-intervention	0.62 (0.25-2.25)	1.38 (0.75-2.50)	**[-1.50; -0.38]; 0.035***	[-1.25; 1.25]; 0.596
Fatigue/Sleepiness (0-4)			U=19.00; p=0.934; r=0.02	
Pre-intervention	1.00 (1.00-4.00)	1.50 (0.00-4.00)		
Post-intervention	1.00 (0.50-4.00)	1.25 (0.50-3.00)	[-0.50; 0.25]; 0.176	[-1.25; 0.75]; 0.518
Neurocognitive/Sensory (0-4)			U=12.00; p=0.376; r=0.26	
Pre-intervention	0.61 (0.22-1.56)	0.83 (0.33-1.44)		
Post-intervention	0.44 (0.00-0.78)	0.56 (0.33-1.11)	[0.78; -0.06]; 0.059	[-0.39; 0.06]; 0.057
Emotional/Psychological (0-4)			U=13.50; p=0.493; r=0.20	
Pre-intervention	1.50 (0.00-4.00)	1.83 (0.00-3.00)		
Post-intervention	1.00 (0.00-3.67)	1.33 (0.67-2.00)	[-0.67; 0.00]; 0.161	[-1.33; 0.33]; 0.789
Respiratory (0-4)			U=9.00; p=0.145; r=0.42	
Pre-intervention	0.00 (0.00-1.33)	0.33 (0.00-1.33)		
Post-intervention	0.00 (0.00-0.00)	0.67 (0.00-1.33)	[-0.83; 0.00]; 0.371	[-0.33; 0.67]; 0.577
Edema/Cardiac (0-4)			U=18.50; p=1.000; r=0.00	
Pre-intervention	0.75 (0.00-2.50)	1.00 (0.00-2.50)		
Post-intervention	0.25 (0.00-4.00)	0.75 (0.00-2.50)	[0.75; 1.00]; 1.000	[-1.00; 0.50]; 0.812
Dermatological (0-4)			U=22.00; p=0.568; r=0.16	
Pre-intervention	0.23 (0.07-0.33)	0.37 (0.00-0.53)		
Post-intervention	0.17 (0.00-0.27)	0.13 (0.00-0.71)	[-0.23; 0.03]; 0.423	[-0.30; 0.16]; 0.418
Bleedings (0-4)			U=17.50; p=1.000; r=0.00	
Pre-intervention	0.00 (0.00-0.00)	0.00 (0.00-0.50)		
Post-intervention	0.00 (0.00-0.50)	0.00 (0.00-1.50)	[0.00; 0.25]; 1.000	[0.00; 0.75]; 1.000
Pain intensity (0-10)			U=20.00; p=0.806; r=0.111	
Pre-intervention	3.5 (0-10)	6.5 (0-10)		
Post-intervention	0.0 (0-3)	1.5 (0-4)	[-5.33; -0.67], 0.066	[-5.33, -1.33], 0.066
Heaviness sensation (0-10)			U=22.50; p=0.518; r=0.250	
Pre-intervention	0.5 (0-9)	5.5 (0-7)		
Post-intervention	0.0 (0-5)	1.0 (0-5)	[-3.67; 1.67], 0.465	[-4.67; 0.33], 0.138
Perceived edema (0-10)			U=23.50; p=0.391; r=0.306	
Pre-intervention	2.0 (0-10)	3.0 (0-10)		
Post-intervention	0.0 (0-6)	1.0 (0-3)	[-3.33; 0.67], 0.276	[-5.17; -0.50], 0.102

Captions: NCI = National Cancer Institute; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; GI = Intervention Group; GP = Placebo Group; CI = confidence interval; Scale 0-4 (higher=worse). Median (min-max). Intragroup Wilcoxon [95% CI], *p* value. Intergroup Mann-Whitney (U, *p*, *r*). Values $p<0.05$ indicated a statistically significant difference.

were fully rescheduled, as planned in the protocol, so the participants who initiated the study missed no treatment sessions. Only one participant did not attend the follow-up assessment one month later, with no impact on the analysis of the assessed outcomes. Therefore, considering the predefined criteria of a minimum of 75% attendance at all sessions, the protocol adherence rate of participants who initiated the protocol was 100%.

Satisfaction of participants presented high scores in both groups, with items that assessed discomfort, frustration, or uneasiness at the minimum of the scale, with no difference between groups (Table 3) (p>0.17).

As exploratory secondary outcomes, pain, heaviness sensation, and perceived edema in the affected upper limb presented a reduction from the period before the intervention to the period after the intervention in both groups. The intragroup and intergroup analyses of this outcome are presented in Table 2, with results described as exploratory, with no confirmatory purpose.

DISCUSSION

The present pilot study aimed at assessing the clinical safety, viability, and acceptability of a multimodal physiotherapeutic supportive care protocol that includes VPBM in women with primary breast cancer in antineoplastic treatment. In general, the findings suggest that the protocol is clinically safe, well tolerated, and viable in the care context, with a high adherence rate and high satisfaction levels among participants. No severe adverse events related to the intervention were observed, although episodes of mild, transitory, and self-limited discomfort have been reported during applications.

Clinical safety constitutes a central aspect of assessing emerging oncology interventions, especially when applied along with conventional antineoplastic treatment. In this study, the multimodal physiotherapeutic protocol, including VPBM, presented a favorable safety and tolerability profile. Although episodes of discomfort, such as nausea and cervical pain, have been observed, these events were classified as mild, transitory, and self-limited, not resulting in the interruption of sessions or the need for additional intervention. Considering the oncological context, in which symptoms such as nausea and pain are often reported as part of the antineoplastic treatment, it is not possible to establish a direct causal relation with the proposed intervention. Still, the occurrence of these symptoms reinforces the importance of systematically monitoring tolerability in clinical trials involving oncological populations.

It is worth underscoring that VPBM was applied within previously established therapeutic parameters with observance of clinical contraindications described in the literature, an essential condition for its utilization in the oncological context. The intervention assessed in this study was structured as a multimodal physiotherapeutic protocol, in which VPBM was integrated into other therapeutic strategies, including manual therapies, kinesiotherapy, respiratory exercise, and self-care guidance. Previous findings describe VPBM as a non-invasive and usually well-tolerated intervention when correctly prescribed[11,13-16,37], a particularly relevant aspect for women in antineoplastic treatment, whose adherence to additional interventions is often limited due to symptomatic overload[6,10]. Despite that, in the present study, no differences were observed between groups that

Table 3. Comparison of mean and standard deviation values regarding satisfaction with the application among the photobiomodulation and placebo groups

Questionnaire	GI (n=6)	GP (n=6)	CI (95%)	*p*
1. In general, I felt satisfied with the application of the resource	4.83±0.40	4.60±0.54	[-0.41;0.88]	0.438
2. I very much liked the resource utilized	4.83±0.40	4.80±0.44	[-0.55;0.61]	0.900
3. I felt frustrated with the application of the resource	1.00±0.00	1.40±0.54	[-1.08;0.28]	0.178
4. I felt angry about the application of the resource	1.00±0.00	1.20±0.44	[-0.75;0.35]	0.374
5. The applied resource was ideal for me	5.00±0.00	4.80±0.44	[-0.35;0.75]	0.374
6. The resource applied met my expectations	4.67±0.51	4.60±0.54	[-0.66;0.79]	0.840
7. I would use this resource again	4.83±0.40	4.80±0.44	[-0.55;0.61]	0.900
8. I would recommend this resource to other people	5.00±0.00	4.80±0.44	[-0.35;0.75]	0.374
9. I found the treatment uncomfortable	1.00±0.00	1.20±0.44	[-0.75;0.35]	0.374
10. I found the treatment too frequent	1.83±1.6	1.80±0.83	[1.77;1.83]	0.968

Captions: GI = Intervention group; GP = Placebo group; CI = confidence interval.
Note: Likert scale from 1 (very dissatisfied) to 5 (very satisfied). Values expressed in mean ± standard deviation. No item showed a statistically significant difference (p>0.05).

allow to infer on a specific effect of VPBM. Therefore, the findings must be interpreted as the result of a set of applied interventions, reflecting both the multimodal character of the protocol and the placebo-controlled design adopted. This characteristic, despite representing a limitation for causal inferences, reflects the actual practice, in which integrated approaches are often utilized in oncology supportive care.

Regarding the self-reported adverse events related to antineoplastic treatments, assessed by the PRO-CTCAE, an intragroup reduction was observed in the pain/musculoskeletal domain during the GI protocol. However, no intragroup differences were identified. Furthermore, the results must be interpreted with caution, considering the reduced sample size and exploratory character of the analyses. These variations do not allow us to infer about the clinical efficacy of VPBM or any component isolated from this intervention and should, therefore, be understood as preliminary signs that can guide further studies with confirmatory designs and greater statistical strength.

From a physiological point of view, the literature describes photobiomodulation as a potential modulator of inflammatory and nociceptive processes through mechanisms such as microcirculation modulation, increase in the bioavailability of nitric oxide, influence on inflammatory mediators, and modulation of neural excitability[11-17]. However, considering the multimodal design adopted in the present study, it is not possible to establish a direct relation between those mechanisms and the observed findings. Moreover, although previous studies in specific clinical populations suggest that VPBM can contribute to managing pain and musculoskeletal symptoms, data available in oncology are still limited and heterogeneous[15,37], reinforcing the need for additional investigations.

The utilization of PRO-CTCAE as a primary safety outcome represents a relevant methodological topic in this study. Instruments based on patient-reported outcomes have been progressively incorporated into clinical research in oncology to allow a direct insight into the subjective experience of patients, often underestimated by traditional clinical assessments[6,7]. Findings suggest that symptoms such as pain, fatigue, and musculoskeletal discomfort are more frequently reported by patients than registered by healthcare professionals, reinforcing the importance of using self-reported instruments to assess the safety, tolerability, and clinical impact of supportive interventions[8].

Another relevant finding was the high adherence rate observed and excellent attendance during the five weeks of intervention, indicating good viability of the protocol in the routine of women in oncological treatment. The literature highlights that supportive interventions must not only be effective but also feasible and acceptable, considering the physical and emotional overload often experienced by this population, characterized by multiple consultations, treatment side effects, and recurrent psychosocial demands[10]. In this sense, integrating VPBM into a multimodal physiotherapeutic protocol, without increasing the duration or complexity of the appointment, may have contributed to the high adherence observed, although it is not possible to isolate the role of each component in the experience of participants.

The high levels of satisfaction observed in both groups reinforce the acceptability of the multimodal physiotherapeutic protocol, regardless of the active or placebo application of VPBM. High scores related to comfort, treatment recommendation, and absence of perturbation reflect a positive perception of the therapeutic experience, in line with contemporary models of integrative care in oncology, centered on patients and integral care[18,19]. The lack of perceptible differences between groups regarding satisfaction suggests that the strategy of applying placebo VPBM was effective in maintaining blindness in the study, strengthening its internal validity, a fundamental aspect in pilot clinical trials with non-pharmacological interventions[31].

Some limitations should be considered when interpreting the results. The reduced sample size, characteristic of pilot studies, limits the statistical power to detect intergroup differences and restricts the generalization of the findings, in addition to increasing the variability of estimations. Moreover, the multimodal nature of the physiotherapeutic protocol prevents attributing the observed effects solely to VPBM, which is, however, a deliberate and coherent choice with the study's objective, centered on assessing the clinical safety, tolerability, adherence, and acceptability of an integrated supportive care model. The secondary outcomes were included as exploratory and must not be interpreted as confirmatory evidence of clinical efficacy.

Despite these limitations, the study has relevant strengths, including its randomized, double-blind design, effective placebo strategy, utilization of validated patient-centered instruments, in addition to being in line with the CONSORT recommendations for pilot and viability studies. These aspects add methodological robustness to the study and provide consistent support for planning large-scale confirmatory clinical trials[28,31,36] to assess the safety and efficacy of multimodal interventions in oncological care.

CONCLUSION

Together, the findings from this pilot study suggest that including VPBM in a multimodal physiotherapeutic supportive care protocol is viable and well-accepted by women with breast cancer in antineoplastic treatment. Although no severe adverse events have been observed, episodes of mild discomfort were recorded during the applications, which indicate the need for caution when interpreting the safety profile. Considering its pilot design, the multimodal nature of the intervention, and the reduced number of participants, it is not possible to draw definitive conclusions regarding the safety of VPBM or attribute specific effects to it. These results reinforce the need for future confirmatory studies with larger samples and robust designs aimed at assessing the safety and clinical efficacy of that approach.

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CONTRIBUTIONS

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DECLARATION OF ARTIFICIAL INTELLIGENCE USE

Artificial intelligence tools were used solely to support wording, linguistic review, and to improve the textual clarity of the manuscript.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data sets utilized and analyzed during the present study are not publicly available due to ethical restrictions related to the confidentiality of participants, since this is a study conducted with human beings in the oncology field. The data can be made available upon request to the corresponding author, conditioned to the ethical norms in force.

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