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Evaluation of vascular photobiomodulation for orofacial pain and tension type headache following COVID 19 in a pragmatic randomized clinical trial

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This pragmatic double-blind randomized clinical trial aims to assess the impact of vascular photobiomodulation on post-COVID-19 patients experiencing tension-type headache, orofacial pain, or both persisting for more than 3 months. Participants were divided into two groups: vascular photobiomodulation (VPBM) and simulated VPBM. Their conditions were evaluated using the Brief Pain Inventory (BPI), Visual Analogue Scale, and Headache Impact Test (HIT-6). Data analysis included both inter and intragroup assessments, employing per-protocol and intention-to-treat analyses. Significant differences were observed in pain levels pre- and post-treatment and between the two groups. These differences were evident in the average pain experienced in the previous week ($p = 0.010$) and various dimensions of the BPI questionnaire, such as the degree of pain interference with walking ($p = 0.011$), work ($p = 0.009$), sleep ($p = 0.012$), and enjoyment of life ($p = 0.016$). However, there was no statistically significant difference in headache impact on activities of daily living as measured by the HIT. Vascular photobiomodulation shows promise in reducing pain and enhancing the ability to engage in daily activities among post-COVID-19 patients experiencing persistent headaches and orofacial pain.

Keywords Covid-19, Facial pain, Photobiomodulation, Intention to treat analysis, Quality of life, Tension-type headache

Abbreviations

ATP	Adenosine triphosphate
ILIB	Intravascular laser irradiation of blood
TTH	Tension-type headache
PBM	Photobiomodulation
VPBM	Vascular photobiomodulation
OFP	Orofacial pain
ICDH-3	International classification of headache disorders
LILT	Low-intensity laser therapy
EDOF-HC	Orofacial pain clinic questionnaire
VAS	Visual Analog Scale

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BPI	Brief pain inventory
HIT-6	Headache impact test
PCR	Polymerase chain reaction

In 2020, the world was caught off-guard by the COVID-19 pandemic, a disease caused by the novel coronavirus (SARS-CoV-2). COVID-19 affected millions of people, causing many deaths from acute respiratory distress syndrome. The clinical course of this disease is characterized by respiratory symptoms and complications. Therefore, the involvement of other systems, such as renal, cardiac, neural, gastrointestinal, and coagulative problems, in this process has been acknowledged.[1]

However, headache is one of the most frequent signs reported by patients with COVID-19.[2] The type of headache attributed to this viral infection is known as tension-type headache (TTH) and migrain, with the tension-type phenotype with bilateral characteristics and pressing quality being the most frequent according to the third edition of the International Classification of Headache Disorders (ICHD-3).[3–28]

Patients started reporting a set of signs and symptoms, including fatigue, dyspnea, "brain fogging" with cognitive disorders, muscular pain and weakness, depression, and persistent headache, after recovery from the acute phase of the disease. A longitudinal study conducted in Brazil, in addition to the described symptoms, demonstrated the persistence of symptoms such as myalgia and arthralgia two years after infection.[27] These signs and symptoms have been collectively called "long COVID-19."[3] Because the characteristics of these signs and symptoms are diverse, the diagnosis of long COVID-19 is challenging. Therefore, long COVID-19 is diagnosed after eliminating other potential causes for these signs and symptoms and based on a history of an early positive polymerase chain reaction (PCR) test or SARS-CoV-2 antigen test.[4]

Headache is the fifth most frequent symptom in patients with long COVID-19, with a prevalence of 18%. Its high prevalence and disabling profile characterize it as a major concern worldwide.[3]

Orofacial pain (OFP) is defined as pain associated with both hard and soft tissues of the head, face, and neck.[5] This includes heterogeneous conditions, and the treatment results depend on multiple factors.[6] The treatment recommended for orofacial pain and headache in general aims to reduce the symptom of pain and restore function. Pain is often controlled through the prescription of analgesic and anti-inflammatory drugs and other adjuvant drugs, which may result in drug interactions from parallel treatments.

Photobiomodulation (PBM), i.e., the use of low-intensity laser, is an option for adjuvant analgesic treatment of TTH. PBM therapy is frequently used to treat various medical conditions, including edema and inflammation, chronic joint disorders, pain, and wound healing.[7]

Isabella et al.[8] state that PBM activates the production of adenosine triphosphate (ATP), nitric oxide, and reactive oxygen species, and improves rheological properties of blood and microcirculation. PBM shows potential action on tissue repair, the modulation of inflammatory processes, and the reduction of oxidative stress, pain, and muscular fatigue.[9]

Clinical and preclinical studies have demonstrated that transcutaneous irradiation of arteries promotes anti-inflammatory and analgesic effects and improves the patients' quality of life. However, it is difficult to access and compare results and consolidate clinical protocols because of the use of various terms in the literature, such as modified intravascular laser irradiation of blood (ILIB), new ILIB, and systemic photobiomodulation, to refer to transcutaneous PBM application. Thus, the term "vascular photobiomodulation" (VPBM) is more specific and uses different light sources and anatomic application sites, such as the radial, sublingual, and carotid arteries.[10]

VPBM has potential analgesic, antispastic, and sedative effects through the stimulation of mitochondrial components, facilitation of blood circulation, and reduction of tissue hypoxia.[11] Thus, the primary objective of this study was to evaluate the effectiveness of VPBM in relieving OFP and TTH in patients who recovered from COVID-19 with the persistence of these symptoms.

Persistent symptoms after infection must be treated with attention and concern for the patient's wellbeing. Therefore, the secondary objectives of this study were to evaluate quality of life before and after this treatment, patient adherence to treatment, and comfort during VPBM application.

Materials and methods

Study design

This was a pragmatic randomized double-blind clinical trial. The trial is part of a broader project within the Graduate Development Program—Pandemic Impacts, supported by the Brazilian Ministry of Education through its Coordination for the Improvement of Higher Education Personnel. It presents the initial findings regarding the effect of PBM on the consequences of the COVID-19 pandemic.

Ethical approval

This clinical trial was approved by the Nove de Julho University Ethics Committee with approval number 4.673.963 and prospectively registered at the Clinical Trial Registry (ClinicalTrials.gov) under No. NCT05430776 (24/06/2022). All patients provided their free and informed consent in writing before entering the study. The design follows the Consolidated Standards of Reporting Trials (CONSORT) international guidelines for randomized clinical trials.

Patients

The patients were recruited at the dental clinic of Nove de Julho University, São Paulo, Brazil. The inclusion criteria were adult individuals of both sexes who aged 18–64 years, had complaints of persistent OFP or TTH for > 3 months since the moment of infection, were diagnosed with COVID-19 confirmed by reverse-transcription PCR (RT-PCR) for SARS-CoV-2, and recovered from the infection at least 30 days prior. The exclusion criteria comprised individuals who presented or reported diagnoses of neuropathy and headache

other than TTH; presented physical or intellectual inability to answer the study's questionnaires; were illiterate individuals, patients with diabetes, pacemaker carriers, pregnant women; and reported laser photosensitivity. Discontinuation criteria included participants who reported any discomfort while the protocols were being conducted, reported sensitivity to laser application, and failed to attend two consecutive consultations.

Sampling

A total of 40 patients participated in the study and were randomized into two study groups, VPBM and sham VPBM groups. The data analysis and follow-up were conducted for 34 participants who underwent at least two interventions.

Procedures

The participants were invited to join the selection procedure, which followed a routine of collection of clinical history, including sociodemographic data such as age, self-reported ethnicity, education, occupation, weight, height, and practice of physical activity, as well as clinical information, including history of systemic diseases, personal and family history of health problems, previously received treatments, and any medication taken at the time of the study. The ICHD-3 questionnaire and the Orofacial Pain Clinic Questionnaire (EDOF-HC) were also administered.

Randomization and allocation

Allocation of participants into the groups was conducted by generating random numeric sequences on a website (www.random.org). The sequence was printed and placed in a sealed opaque envelope. Only one researcher had access to the sequencing. After allocation, the participants answered the evaluation questionnaires.

Interventions

Data collection took place from October 30, 2022, to March 30, 2023. The participants were received in a private room free of sound interference and seated on a clinical chair with support and stabilization of the left arm, where the laser-emitting equipment was fixed. At the moment of application, only the volunteer and the researcher responsible for the treatment were present.

The VPBM group received the treatment of vascular photobiomodulation using the ECCO Reability device (Eccofibras, São Paulo, Brazil), which has a red wavelength of 660 ± 10 nm and a power of 100 mW. The recommended application time of the device was 30 min, as presented in Table 1. The sham VPBM group underwent applications of the same duration, but the device used emitted light with inactive PBM. The device was positioned with the spot focused on the participant's left radial artery and fixated to the wrist using a specific wristband.

The total duration of treatment was four weeks with a weekly frequency, totaling four sessions.

Procedures to ensure double blinding of assessments

The assessments (both before and after VPBM application) were performed by the researcher, who was not informed about the group to which each participant was allocated. The participants did not know whether they received VPBM, as the placebo device emitted a conventional red light, and the device's characteristic sound was preserved and was identical to that of the active device, so that the participant could not detect any difference. The device ended the protocol automatically after a 30-min period of application.

Outcome measures

The outcomes of interest were assessed both before the intervention and during its execution. The following assessments were conducted to measure the primary outcome:

Pain assessment

The short form of the Brief Pain Inventory (BPI) was administered weekly. This is a multidimensional questionnaire that uses a scale from 0 to 10 to measure pain intensity and its interference on the ability to walk, conduct daily activities, work, and perform social activities, as well as on mood and sleep. The patient rated the

Parameters	Red laser (systemic transcutaneous)
Wavelength (nm)	660
Operating mode	Continuous
Power (mW)	100
Exposure time (s)	1800
Energy (J)	180
Number of irradiated spots	Systemic
Application technique	Contact
Number of sessions	4
Treatment frequency	Once a week
Total irradiated energy (J)	1440

Table 1. Dosimetry parameters of photobiomodulation application.

pain experienced at the moment of answering the questionnaire, as well as the most intense, the least intense, and the mean pain experienced in the previous 24 h.

The Visual Analog Scale (VAS) for pain is a unidimensional instrument for assessing pain intensity. It consists of a line with its extremities numbered 0 to 10. "No pain" is marked at the former extremity, and "the worst pain imaginable" is marked at the latter. The patient is then asked to evaluate and mark on the line the pain experienced at that moment. The VAS was administered at each session's start and end.

Impact of headache on activities of daily living assessment

The Headache Impact Test (HIT-6) was used to assess the impact of the protocols used to treat headaches on patients' ability to perform activities of daily living. The HIT-6 was administered during the initial evaluation and during the last session, according to the study protocol. This test is easy to administer, reliable, and validated for the Brazilian context.

The HIT-6 comprises six questions in the domains of pain, ability to perform daily activities, social functioning, energy/fatigue, cognition, and emotional stress. The score for each question is calculated based on a value of 6 points when the answer is "never," 8 points for "rarely," 10 points for "sometimes," 11 points for "very often," and 13 points for "always." The total score ranges from 36 to 78. Scores < 49 points suggest that headache has little to no impact on the patient's quality of life. Scores from 50 to 55 points mean that there is some impact on daily activities, but the individual can still perform those activities normally. Scores from 56 to 59 points indicate substantial impact, i.e., it is difficult for the patient to perform daily activities due to the pain. Scores > 60 points show a very severe impact on the quality of life, leading to the inability to perform daily activities.

Intake of analgesics

A medication reminder was also used to collect information on the medication taken by the patient, including the need to take analgesic medication, change the existing medication, or introduce new medication other than that usually taken. The decision to use this tool was related to the pragmatic nature of this study, which involves the participants not being prevented from taking analgesic medication and being instructed to continue with their normal habits and activities to ensure that real information on the applicability of VPBM was obtained.

Statistical analyses

The data were analyzed using two approaches for inter- and intragroup comparisons. First, a per-protocol analysis (PPA) included only the data from participants who adhered fully to the study protocol, evaluating treatment efficacy. Second, an intention-to-treat (ITT) analysis set was employed, comprising all randomized patients who attended at least two treatment sessions, with data imputed using the "last observation carried forward" method. Clinical data variables were analyzed with IBM SPSS Statistics software (IBM Corporation, Armonk, NY, USA) for Windows. For non-normally distributed data, as determined by the Shapiro–Wilk test, the Mann–Whitney U test was used for between-group comparisons, while the Wilcoxon signed-rank test was used for comparisons across different study periods. For normally distributed data, a repeated-measures ANOVA was applied to assess differences within and between groups across the study time points, followed by Bonferroni post hoc tests to adjust for multiple comparisons between groups. Categorical variables were analyzed using chi-square and Fisher's exact tests, as appropriate. Statistical significance was set at $\alpha = 0.05$.

Results

A total of 40 patients participated in the study from October 30, 2022, to March 30, 2023, and were randomized into two study groups, VPBM and sham VPBM groups. The data analysis and follow-up were conducted for 34 participants who underwent at least two interventions. Table 2 describes the participants' characteristics in relation to the groups at the beginning, before the first intervention.

	VPBM group (n = 14)				**Placebo group (n = 20)**				***p*-value**
Age	44.29 (SD = 12.7)				40.25 (SD = 11.5)				0.346
Sex	Female		Male		Female		Male		0.299
	92.9% (n = 13)		7.1% (n = 1)		80.0% (n = 16)		20.0% (n = 4)		
Initial pain (VAS)	3.42 (SD = 1.500)				3.13 (SD = 1.505)				0.615
HIT- 6 (impact on quality of life)	Little impact	Some impact	Substantial impact	Severe impact	Little impact	Some impact	Substantial impact	Severe impact	0.543
	8.3%	25%	0	66.7%	6.3%	2%	12.5%	68.8%	
Hospitalization due to COVID-19	Yes		No		Yes		No		0.635
	7.1% (n = 1)		92.9% (n = 13)		10% (n = 2)		90% (n = 18)		
Recovery time from COVID-19 (months)	Mean		SD		Mean		SD		0.958
	12.93		9.61		13.10		9.15		

Table 2. Characteristics of the participants at the start of the study. VPBM, vascular photobiomodulation; HIT-6, Headache Impact Test-6; SD, standard deviation.

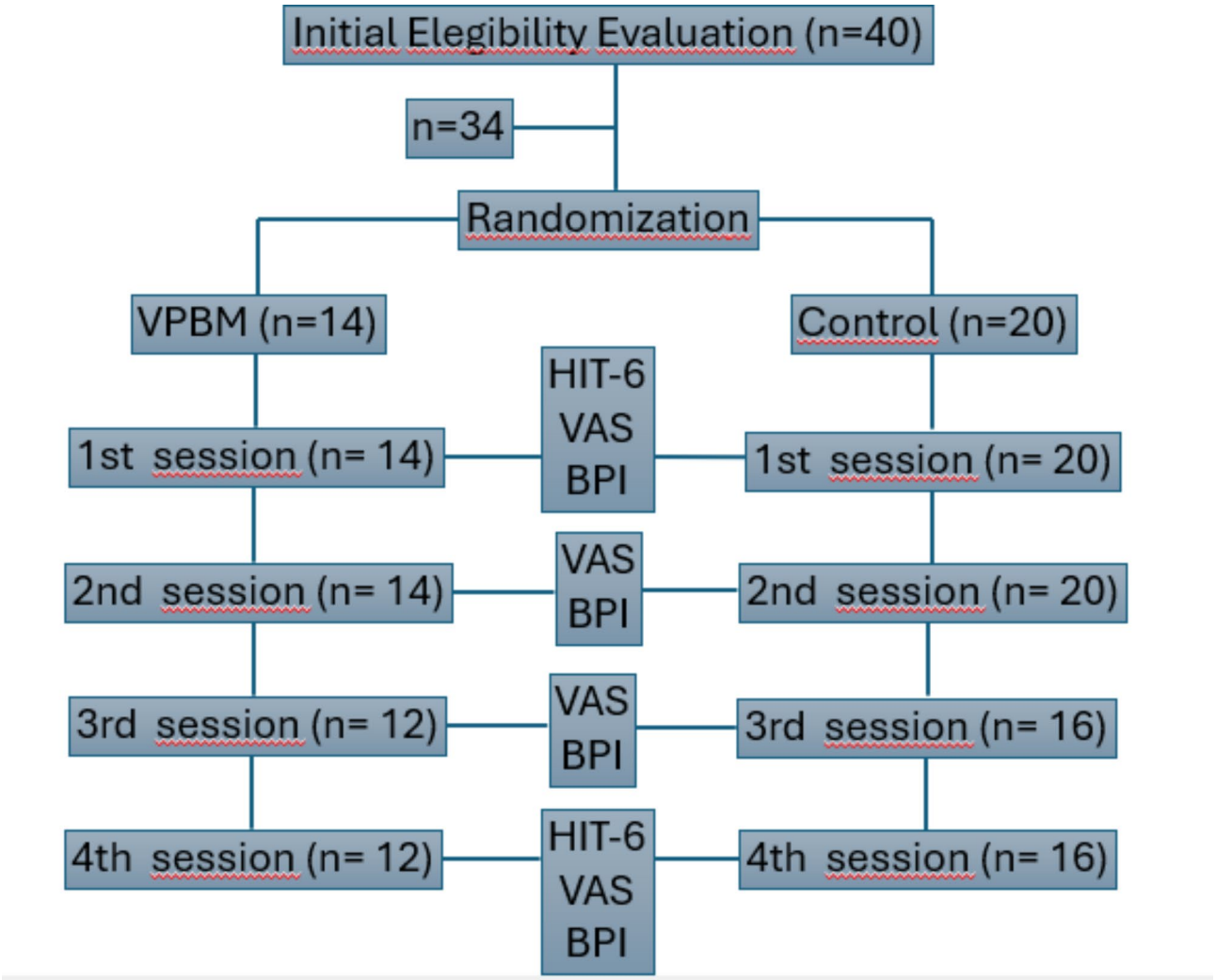

Fig. 1. Patient flowchart. BPI, Brief Pain Inventory; VAS, Visual Analog Scale; HIT-6, Headache Impact Test.

	VPBM group (n = 12)	Placebo group (n = 16)	*p*-value (within groups)	*z*-value
VAS before	3.42	3.13	< 0.001*	− 3,077
VAS after	0.33	1.38	0.002*	− 2,458
p-value (between groups)	0.001*			

Table 3. Comparison of response to pain by the Visual Analog Scale within and between the groups, before and after the four treatment sessions. *statistically significant, $p < 0.05$, Wilcoxon and Mann–Whitney U tests.

Per-protocol analysis

The following analyses represent the comparison of the participants who were randomized into the study groups and underwent all four interventions and the follow-up, according to the initially proposed protocol. Figure 1 illustrates the study flowchart and the number of participants in each group during the protocol and follow-up.

A total of 28 participants underwent the complete intervention, of which 12 were in the VPBM group and 16 in the sham VPBM group. The comparison of the sensation of pain as measured by the VAS before and after each of the four sessions in each group showed a significant improvement in both groups during follow-up ($p < 0.001$ for the VPBM group and $p = 0.002$ for the sham VPBM group). The comparison of pain improvement between the two groups showed a significant difference ($p = 0.001$), with a greater difference between the scores before and after treatment in the VPBM group (Table 3).

Figure 2 shows the pain sensation reported by the participants after all four sessions in each group. Pain was reduced in both groups, but pain reduction was consistent and gradual, and it remained at the lowest grade of the scale after the last session. Pain reduction was also reported in the sham VPBM group; however, after the last session, the pain increased to a level higher than that reported after the second session.

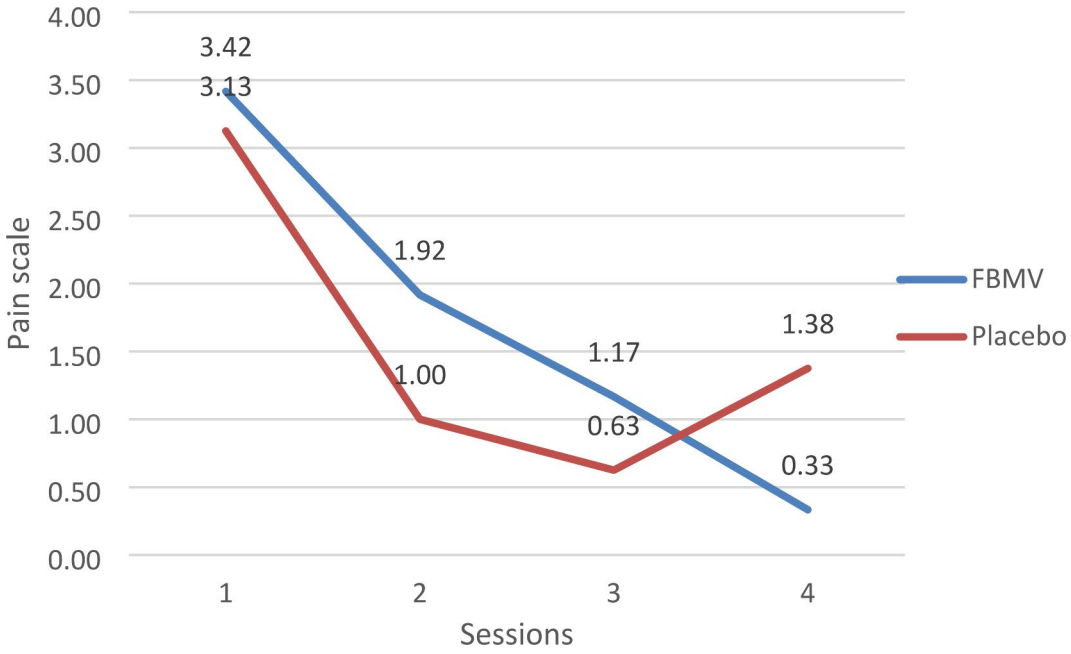

Fig. 2. Pain sensation reported by participants after each of the four sessions in each group.

	Value of the test	F statistic	p-value
Hospitalization	**0.040**	**0.485**	**0.622**
Recovery time	0.014	0.169	0.846

Table 4. Multivariate analysis of factors "need for hospitalization" and "recovery time" relative to the two groups.

Factors	Dependent variable	Sum of the squares	Mean square	F	*p*-value
Hospitalization	Pain before	2.361	2.361	1.007	0.326
	Pain after	0.074	0.074	0.126	0.726
Recovery time	Pain before	0.082	0.082	0.035	0.853
	Pain after	0.208	0.208	0.352	0.558
Group	Pain before	0.300	0.300	0.128	0.723
	Pain after	7.290	7.290	12.368	0.002*

Table 5. Analysis of factors "need for hospitalization" and "recovery time" relative to reduction of pain at the end of the treatment.

For factors related to COVID-19, such as need for hospitalization and recovery time, the multivariate analysis showed no association of having been hospitalized and recovery time with pain reduction in either group (Table 4). When pain reduction was considered a dependent variable, these factors also did not affect pain after the four sessions in either study group (Table 5).

The Impact of headache on activities of daily living, as measured by the HIT-6, showed that 66.7% of the patients in the VPBM group and 68.8% of those in the sham VPBM group reported a severe impact of headache on their activities of daily living. There was a reduction in the impact after the four protocol sessions in both groups, but it was not statistically significant (Table 6).

The answers to the BPI questionnaire were compared both within and between the groups. In the VPBM group, there was a significant reduction in the scores of the questions on the mean pain experienced in the previous week ($p = 0.010$) and on the degree of interference of pain with walking ($p = 0.011$), working ($p = 0.009$), sleeping ($p = 0.012$), and enjoyment of life ($p = 0.016$), as shown in Table 7.

Intention-to-treat analyses

The ITT analysis of pain sensation using the VAS showed a significant reduction between the start and the end of the treatment in both groups, but no statistically significant difference was found between the groups ($p = 0.189$).

			Initial HIT-6					
			Little impact	Some impact	Substantial impact	Severe impact	Total	Intergroup p-value
Group	VPBM	n	1	3	0	8	12	
		%	8.3%	25.0%	0.0%	66.7%	100.0%	
	Placebo	n	1	2	2	11	16	0.543
		%	6.3%	12.5%	12.5%	68.8%	100.0%	
Total		n	n	5	2	19	28	
		%	%	17.9%	7.1%	67.9%	100.0%	
			Final HIT-6					
			Little impact	Some impact	Substantial impact	Severe impact	Total	Intergroup p-value
Group	VPBM	n	3	1	3	5	12	0.770
		%	25.0%	8.3%	25.0%	41.7%	100.0%	
	Placebo	n	4	3	2	7	16	
		%	25.0%	18.8%	12.5%	43.8%	100.0%	
Total		n	7	4	5	12	28	
		%	25.0%	14.3%	17.9%	42.9%	100.0%	
		VPBM	0,093					
Intragroup p-value		Placebo	0,302					

Table 6. Intergroup and intragroup association of the impact of headache on quality of life before and after the treatment.

	Group	n	Before	After	*p*-value	*Intergroup p*-value
Maximum pain in the previous week (1 to 10)	VPBM	12	5.83 (3.38)	5.08 (3.55)	0.966	0.601
	Placebo	16	4.00 (3.14)	2.94 (2.48)	0.900	
Minimum pain in the previous week (1 to 10)	VPBM	12	2.92 (2.15)	2.33 (2.70)	0.366	0.163
	Placebo	16	1.75 (1.65)	1.13 (1.25)	0.594	
Mean pain in the previous week (1 to 10)	VPBM	12	5.00 (2.94)	3.58 (2.46)	**0.010***	**0.041***
	Placebo	16	3.88 (2.08)	2.00 (1.56)	0.086	
Pain at the moment (1 to 10)	VPBM	12	3.67 (2.18)	2.83 (2.44)	0.099	0.495
	Placebo	16	2.06 (2.14)	1.19 (2.16)	0.398	
Pain relief with medication (0% to 100%)	VPBM	12	1.83 (2.65)	1.83 (2.85)	0.547	0.515
	Placebo	16	1.56 (2.52)	0.69 (1.49)	0.804	
General activity (0 to 10)	VPBM	12	2.67 (3.93)	1.83 (2.82)	0.156	0.738
	Placebo	16	2.44 (3.40)	1.06 (2.54)	0.853	
Stamina (0 to 10)	VPBM	12	5.00 (3.79)	2.67 (2.47)	0.531	0.248
	Placebo	16	4.25 (3.97)	1.44 (2.89)	0.962	
Ability to walk (0 to 10)	VPBM	12	2.67 (3.47)	1.42 (2.39)	**0.011***	**0.011***
	Placebo	16	1.56 (3.38)	0.44 (1.20)	0.509	
Normal work (0 to 10)	VPBM	12	3.83 (3.76)	1.58 (2.93)	**0.009***	**0.021***
	Placebo	16	2.94 (3.56)	0.75 (2.08)	0.232	
Relations with other people (0 to 10)	VPBM	12	4.17 (3.95)	1.75 (3.51)	0.098	0.227
	Placebo	16	4.56 (3.89)	0.81 (2.56)	0.309	
Sleep (0 to 10)	VPBM	12	4.92 (4.02)	2.92 (3.37)	**0.012***	0.082
	Placebo	16	2.19 (3.50)	0.50 (1.41)	0.568	
Enjoyment of life (0 to 10)	VPBM	12	3.67 (3.82)	2.17 (2.94)	**0.016***	**0.043***
	Placebo	16	3.31 (3.36)	2.50 (1.50)	0.942	

Table 7. Answers to the BPI questionnaire before and after treatment in both groups. BPI, Brief Pain Inventory. *Statistically significant difference, $p < 0.05$.

Figure 3 presents pain response according to VAS in both groups for the four treatment sessions, considering the ITT analysis. A trend toward pain reduction was observed in both groups, but no difference was observed between them.

In the ITT analysis, COVID-19 recovery time and need for hospitalization due to the infection also did not interfere with pain response in either group.

The impact of headache on activities of daily living, considering all participants who underwent at least two treatment sections, also did not show any significant difference between the groups both before and after treatment.

Discussion

Long COVID-19 is a set of symptoms that persist for weeks or months after recovery from the acute COVID-19 infection. The symptoms are varied, and individuals can experience muscular fatigue, dyspnea, muscular pain and weakness, "foggy brain" sensation, depression, psychiatric disorders, and even persistent headache. Both pharmacological and non-pharmacological treatments are used to contain these symptoms; however, because long COVID-19 is a new pathological condition, studies that direct its treatment are still lacking.

VPBM is a resource used as an adjuvant treatment in controlling pain and in modulating inflammation. The present randomized double-blind clinical trial aimed to evaluate the effectiveness of VPBM in relieving pain in patients with persistent post-COVID-19 headache. A total of 34 participants who underwent at least two interventions were included after being randomized and included in either VPBM treatment or its simulation (sham VPBM). When their data were analyzed together, it was not possible to determine a statistically significant difference between the intervention and control groups, with the sample showing a Gaussian distribution between the groups.

The primary outcome analyzed in the PPA (data of those patients who finished all four treatment sessions) showed a significant improvement in pain sensation compared by VAS before and after the four sessions in both groups (treatment and placebo). The improved pain sensation in the sham VPBM group may be associated with other pain mechanisms related to TTH such as a compromised musculoskeletal system, namely a greater tension in the pericranial muscles and the emotional aspects involved in pain, which were mitigated by receiving the treatment for 30 min in a relaxing position and by the humanized reception in all sessions[12–14]

When the reduction in pain sensation was analyzed per session, a gradual, consistent, and progressive reduction was observed in the treatment group, with the treatment leading to a lower score on the scale after the last session. These results are consistent with those found in the literature regarding the effects of VPBM and the plausible causes of persistent post-COVID-19 TTH. Although these causes are not well established yet, some studies hypothesize that SARS-CoV-2 may trigger a hyperinflammatory state by increasing proinflammatory cytokines, and that a situation of hypoxia, hypercapnia, or both can cause a persistent activation of the immune system with a biohumoral response.[3,15]

For the effects of VPBM, some studies have demonstrated its action on the superoxide dismutase enzyme, resulting in restricted production of prostaglandins from arachidonic acid by cyclooxygenase-2, thus leading to a systemic block of the inflammatory process. Additionally, VPBM stimulates mitochondrial components, thereby producing positive effects on immunoglobulins, interferons, and interleukins; it facilitates blood circulation; it increases the oxygen difference between arteries and veins, acting on tissue hypoxia and improving the oxygen

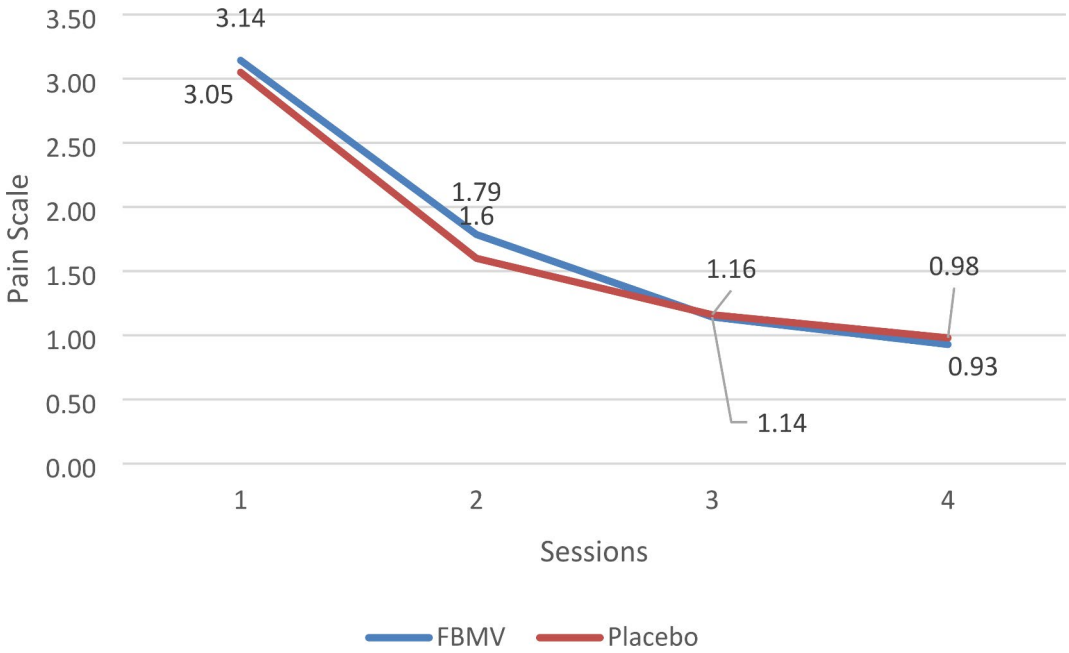

Fig. 3. Response to pain on the Visual Analog Scale in both groups in the four weeks of treatment.

intake; and it also increases the oxygenation of molecules such as glucose and pyruvate, leading to an increased synthesis of ATP.[16,17]

A reduction in the pain scores was also observed in the sham VPBM group, but in the last session, the score on the pain scale was higher than that in the second session, which demonstrates the absence of persisting effect because this group did not receive the benefits of PBM, such as the modulation of the inflammatory process. Therefore, the causal factor of pain was not treated, and the pain reported initially tended to return.

The ITT analyses (including data from patients who did not finish the protocol but underwent at least two sessions) showed the same behavior of pain sensation reduction when comparing the scores from the first and last sessions both in the VPBM group and in the sham VPBM group. The assessment of pain sensation through VAS in each session showed a trend toward pain reduction in both groups but with a very small difference between the second, third, and last sessions.

This trend can be explained by the type of analysis performed, in which data from those patients who did not complete the protocol and attended only up to the second session are replicated. The reasons for abandoning the study were related to conditions of daily living, such as changes in work schedule, start of new work activities, transportation difficulties, financial difficulties in transportation, and family problems. It is not known whether the cases of study abandonment were due to lack of efficacy against pain before the protocol conclusion in the VPBM group, considering that PBM involves a long and gradual process of inflammation modulation and analgesic effects at the cell level, or due to the lack of efficacy from the absence of actual treatment in the sham VPBM group.

For the factors related to COVID-19 such as need for hospitalization and recovery time, neither the per-protocol nor the ITT multivariate analysis showed any differences regarding these variables in relation to pain reduction in either group, which demonstrates that these factors did not interfere with pain response at the end of the four sessions. Regarding the persistence of general symptoms in long COVID-19, studies have demonstrated a similarity between outpatients and hospitalized patients.[18] For the correlation between headache and disease severity, a retrospective cohort study by Poncet-Megemont et al.[19] evaluated and followed up outpatients and hospitalized patients positive for COVID-19 for 1 month and did not find an association between headache and disease severity. Silva et al.[27] report a consistent prevalence of long COVID across various levels of severity, age groups, and comorbidities.

The secondary outcome "Impact of Headache on Activities of Daily Living" was assessed using the BPI and HIT-6 validated questionnaires. The initial PPA of the data measured by the HIT-6, which reflects the impact of headache on activities of daily living, showed a severe impact on both groups (66.7% in the VPBM group and 68.8% in the control group). Mutiawati et al.,[20] in a cross-sectional study involving 215 patients, observed a worsening quality of life due to headache among > 20% participants. The high percentage of reports of severe impact on quality of life shows a condition of suffering, because headache is disabling and prevents routine activities, impairs performance at work, increases socioeconomic costs, and is considered a public-health problem, in addition to leading to a higher risk of excessive use of analgesics and other drugs.[13]

After the full administration of the protocol (four sessions), the impact on the activities of daily living was reduced in both groups; however, the reduction was not significant in either the per-protocol or the ITT analysis. This may be related to the short follow-up period and evaluation, as studies that assess impact on health using results reported by patients usually include three different evaluation stages such as the start of the study, 2 weeks into the study, and 12 weeks into the study.

Another issue is the limitations of the validated HIT-6 questionnaire regarding the emotional, symptomatic, and social impact of headache.[21] Gutiérrez-Canales et al.[18] evaluated the quality of life and the persistence of symptoms in outpatients after recovery from COVID-19. Their sample had 206 patients divided into two groups, one with patients whose symptoms persisted for ≤ 5 months and another with patients whose symptoms persisted > 5 months. Using the validated SF-36 questionnaire, which comprises 36 items that aim to measure eight dimensions, the authors concluded that most patients presented persisting symptoms after recovering from COVID-19, and the most common symptoms were fatigue, anxiety, and headache. The most affected parameters were mental health, vitality, and changes in health, factors that we believe affect the patients' daily activities, such as working and performing general activities, in addition to their sleep quality.

The results obtained herein are consistent with those reported by Zhou et al.,[22] who used the same method to evaluate 120 patients over one year after hospital discharge and observed a significant reduction in functional capacity and general health. Moreover, COVID-19 survivors reported greater difficulty sleeping.

The Brief Pain Inventory (BPI) is a comprehensive tool used to assess pain experienced by patients both during evaluation and over the preceding 24 h, highlighting the impact of pain on daily activities. Certain dimensions evaluated within the BPI exhibit a significant influence on an individual's ability to walk, work, sleep, and enjoy life. A noteworthy reduction in scores was observed in the VPBM group when comparing data collected from the initial session to those obtained in the final session, particularly in areas concerning the average pain experienced in the previous week and the interference of pain during essential activities such as walking, working, sleeping, and enjoying life—all of which directly affect an individual's quality of life. This pattern remained consistent in the intention-to-treat (ITT) analysis.

Furthermore, Silva et al.[27] assessed Brazilian patients two years post-infection, revealing qualitative changes in the execution of daily activities, work, and social/leisure activities. These changes were associated with a negative impact on the quality of life of these patients. Salehpour et al.,[23] in a narrative review, stated that PBM can cause changes at the behavioral level, including cognitive improvement, antidepressant effects, and improved sleep quality, through its effect of stimulating the mitochondrial electron transport chain, increasing the mitochondrial membrane potential and oxygen consumption, and therefore increasing the proton gradient and ATP production.[23] There is also an increase in the brain blood flow, energetic metabolism, antioxidant

defenses, and modulating antiapoptotic and proapoptotic mediators and inflammatory signaling and stimulating neurotrophic factors that promote neuron protection and survival.

Some studies demonstrate improved sleep duration, efficiency, and quality after VPBM therapy.[24] Eshaghi et al. observed a significant increase in serotonin levels in some brain regions of mice exposed to PBM.[25] Serotonin has an important action on the brain regions that regulate sleep and awakening.

We believe that the improved ability to walk may be related to the positive effects of VPBM on muscle conditions, as shown by Jankaew et al. in their controlled study with 48 participants with knee osteoarthritis.[26] After 8 weeks of PBM therapy, the patients in that study showed improvement in knee extensor muscle strength and in performing activities such as standing up and brisk walking and taking less time to climb stairs.

Limitations and future scope of the study

The results of the present study should be interpreted considering its limitations. Although headache and OFP due to long COVID-19 have gained attention in recent times, there are no studies reporting on the treatment of these conditions in the literature, thus making it difficult to determine an ideal sample size. On the other hand, the results of this convenience sample may help plan future clinical trials on this subject. Another potential limitation is the definition of a protocol that is specific for the condition under treatment, as this is the first clinical trial of VPBM for the treatment of headache and OFP related to COVID-19. Despite these limitations, the clinical and methodological information from this study can contribute to reflection and foster new studies on this subject.

Conclusion

VPBM demonstrated significant pain reduction in individuals experiencing orofacial pain (OFP) and tension-type headache (TTH) following COVID-19, in comparison to a simulated treatment (placebo). Moreover, it notably diminished the interference of pain in crucial activities such as walking, working, sleeping, and enjoying life. By enhancing the performance of these daily activities and improving sleep quality, VPBM directly contributes to enhancing individuals' overall quality of life.

Data availability

The data collected and analyzed during this research are not publicly available to ensure the integrity and reliability of the obtained results, thereby ethically guaranteeing the protection of research participants, respecting the confidentiality agreement of the informed consent form. This approach also ensures that the data are used, interpreted, and understood within the real context of the research. The raw data and analyses can be accessed upon request to the corresponding author. The data are stored on the Harvard Dataverse platform (https://doi.org/10.7910/DVN/OATKWD) and can be accessed with permission from the corresponding author.

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Author contributions

M.C.V.C., S.S.V.S., A.J.L., A.C.M., T.S., F.C.S., M.D.M., K.P.S.F., E.S.F., R.A.M.F., A.C.R.T.H., S.K.B., and L.J.M. participated in the conception and design of the study. S.S.V.S., M.C.V.C., A.J.L., A.C.M., and T.S. participated in the data collection and drafted the manuscript. E.S.F. and L.J.M. performed statistical analysis. S.S.V.S., F.C.S., M.D.M., K.P.S.F., R.A.M.F., A.C.R.T.H., S.K.B., and L.J.M. critically reviewed the manuscript for intellectual content. L.J.M. coordinated the study. All authors read and approved the final protocol.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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