Original Research Article

Exploring Photobiomodulation Therapy for Long COVID Xerostomia: A Randomized Controlled Pilot Trial

ABSTRACT

Aims: To investigate the effects of a photobiomodulation protocol in the treatment of long COVID-19 xerostomia

Study design: This is a single-center, randomized, controlled, double-blind pilot clinical trial.

Methodology: 10 patients with long COVID-19 xerostomia are randomized into two groups. The participants receive a standard xerostomia treatment and also a low-intensity photobiomodulation therapy or placebo photobiomodulation therapy on the cutaneous topography of the salivary glands (a RED LED cluster, 2 J/cm^2, 108 J per session, twice a week for six weeks**.** The outcomes measured using the Oral Health Impact Profile (OHIP-14), Xerostomia Inventory (XI) Scale, Brazilian version of SF-36 Quality of Life Scale, Brazilian Version of Functional Independence Measure (FIM), sialometry and salivary pH before and after the therapeutic period of six weeks of intervention.

Results: there were no significant differences between the photobiomodulation and placebo groups in the baseline or post-intervention moments for evaluated outcomes. In the individual analysis of the OHIP-14 and XI items, a difference was observed in the values of the PBM group comparing the pre-intervention baseline moment with the post-intervention PBM moment, not founded in the placebo group. No adverse effects are reported. **Conclusion:** This PBM protocol was not superior to placebo in treating long COVID xerostomia for the evaluated outcomes. This study has limitations such as the small sample size and unblinding issues, which may have leading to a lack of significant results for primary outcomes in both the PBM and placebo groups. PBM irradiation of the salivary glands could be studied as a future approach to improving saliva production in patients with xerostomia due to long COVID.

Keywords*: Xerostomia, Photobiomodulation, Low level laser therapy, long COVID.*

1. INTRODUCTION

Xerostomia is defined as a subjective sensation of dry mouth described by patients. It is often associated with hyposalivation (reduced salivary flow rate) [1]. Several common oral consequences of dry mouth are reported, including altered taste, difficulty in eating, chewing, and swallowing, halitosis, chronic burning sensation, and intolerance to spicy foods. These changes can lead to altered food and fluid choices, potentially compromising nutritional status. Xerostomia also increases the risks of choking and aspiration pneumonia [2].

The sensation of dry mouth is a complex condition, reflecting a physiological deficiency with or without perceived dysfunction in the volume and molecular composition of saliva [3]. Oral dryness can be caused by many factors, accompanied by complaints across a wide clinical spectrum, with distinct pathophysiologies depending on the etiology. The reported prevalence of xerostomia in the literature from various etiologies ranges from 10% to 80% [4]. A condition currently under study is long COVID-19 xerostomia.

Different descriptions of long COVID have already been proposed. The term "long COVID-19" is commonly used to describe a broad range of signs and symptoms that persist or develop after acute COVID-19, lasting at least two months after the initial infection and not attributable to other underlying diseases [5]. The mechanisms involved in the development of long COVID are still not fully understood, and current explanations should be considered as theories rather than established evidence.

Hypothesis are based on a combination of pathophysiological mechanisms mediated by a set of individual risk factors such as biological sex, severity of acute illness, symptoms during the acute phase, residual tissue damage from infection, increased presence of tissue angiotensin-converting enzyme 2 (ACE2), continuous immune stimulation from reservoirs of persistent infection, chronic disruption of immune subsets after contamination, altered Aquaporin Activity and the activation of an heightened autoimmune response following acute infection [6, 7].

High heterogeneity has been found among studies concerning clinical symptoms manifestations of long COVID. Regarding the mouth, oral cavity, and nasopharynx, the most common manifestation was altered taste, followed by xerostomia and oral ulceration, with grouped prevalence rates of 48%, 35%, and 21%, respectively. Given the possibility of persistent oral dysfunctions after COVID-19 recovery, hospital discharge should not be seen as the end of COVID treatment. Long COVID is a syndrome that demands resources, and the presence of oral changes such as xerostomia when not properly treated, can increase the cost of follow-up [8].

Primary approaches in the initial treatment of xerostomia involve behavioral and adaptive measures for symptom control, prevention of complications, and reduction of hyposalivation. These include careful dental evaluation emphasizing proper oral hygiene, the use of low-sugar diets, daily topical fluoride, antimicrobial rinses for the prevention of dental caries, and oral hydration. Patients should be encouraged to make lifestyle changes, such as quitting smoking, reducing consumption of caffeine-containing beverages, and preventing mouth breathing. They should also receive balanced nutritional guidance [3]. Additionally, strategies aimed at alleviating dry mucosa and dysphagia are recommended, such as the use of oral lubricants, artificial saliva, measures for aspiration prevention, and careful use of liquids during meals [9].

Concurrently**,** studies demonstrate that photobiomodulation therapy (PBM) is often used in the treatment of oral diseases and presents itself as a non-invasive, low-cost, safe therapy that benefits the quality of life of these patients. Photobiomodulation refers to a series of therapies in which non-ionizing light beams, including lasers, LEDs, and broadband light in the visible and infrared spectra, interact with biological tissues for different purposes. This includes electromagnetic radiation, unidirectional, monochromatic, narrow-beam, parallel propagation (collimation), and photon waves in phase (coherence) [10–13].

Numerous photobiomodulation techniques have been employed in the treatment of oral mucosal lesions, and clinical studies have investigated their efficacy specifically for the treatment of xerostomia from various etiologies [14–21], making this technique a therapeutic option for the treatment of xerostomia also arising from COVID-19.

Photobiomodulation can increase the number of ducts, epithelial cell mitosis, protein synthesis, glandular blood circulation, salivary flow rate, and tissue healing, while reducing inflammation [22]. These effects are crucial for its use in the treatment of salivary secretion disorders and xerostomia symptoms.

However, although the usefulness of PBM in the treatment of xerostomia and hyposalivation is established through intraoral or transcutaneous stimulation in the topography of salivary glands, studies applying PBM specifically to treat xerostomia or hyposalivation resulting from COVID-19 are lacking.

Based on these premises, this pioneering study aimed to investigate the clinical efficacy of a photobiomodulation protocol in the treatment of long COVID-19 xerostomia.

2. MATERIAL AND METHODS

2.1 Design

This is a single-center, randomized, controlled, double-blind pilot clinical trial involving 10 patients with long COVID-19 xerostomia recruited at the University hospital during the year 2023. This study complies with the CONSORT Statement for clinical trials [23] and adheres to research ethics guidelines in accordance with the Declaration of Helsinki. The research protocol for this study was registered prior to data collection on the Clinical Trials website (https://clinicaltrials.gov/) under registration number NCT05760092. The study did not interfere with the clinical monitoring and medical decisions of the healthcare team or the patient's medical routines.

2.2 Participants

Ten adult patients with long COVID-19 after laboratory-confirmed acute SARS-CoV-2 infection, presenting xerostomia after SARS-CoV-2 acute infection and persisting for at least 2 months not explained by concurrent alternative diagnoses. Xerostomia was clinically assessed during the first in-person evaluation at the University, based on the study by Fantozzi et al. [24] and following the criteria published by Löfgren et al. [25] comprising xerostomia as the subjective sensation of oral dryness reported by the patient.

2.3 Exclusion Criteria

- Patients with pre-existing conditions presenting xerostomia before SARS-CoV-2 infection.
- Patients without a defined diagnosis, even if they have symptoms and complaints consistent with long COVID-19.
- Previous use in the last 90 days of Laser or other PBM techniques for the same or other indications.
- Systemic inflammatory diseases (rheumatoid arthritis, Reiter's syndrome, ankylosing spondylitis, generalized polyarthritis, neoplasms), uncontrolled previous metabolic or endocrine disorders.
- Severe cognitive or psychiatric disorders requiring psychiatric care or impairing study understanding and psychosocial disorder preventing adherence to treatment.
- Steroid injections within the last 48 hours prior to the initial study assessment.
- Use of immunosuppressive corticosteroid at dose (20 mg daily of prednisone or equivalent for at least 14 days).
- Infection or tumor at the site of therapy application.
- Signs, symptoms, or laboratory changes suggestive of acute COVID-19 reinfection.

- Any photosensitive disease or light-sensitive condition.
- Pregnancy.

2.4 Randomization, Allocation, and Blinding

After obtaining informed consent from all patients, those included in the study were randomized and allocated to one of the two study groups. Patients were assigned to the two groups using randomization in the online software Research Randomizer (https://www.randomizer.org/), which generates a random, sequential list for randomization. Participants were randomized into two groups: the intervention group [PBM therapy + standard treatment for xerostomia] and the control group [Placebo PBM therapy + standard treatment for xerostomia].

The participant was allocated to the corresponding group based on the randomization list, and only the evaluator responsible for the allocation and therapy application knew which group the patient belonged to. At the time of allocation, opaque envelopes were labeled with sequential numbers, each containing information about the corresponding experimental group according to the randomization list order. The envelopes were sealed and remained sequentially numbered until the treatment phase. Immediately prior to treatment, the researcher responsible for administering the treatment would open an envelope (without altering the numerical sequence) and proceed with the indicated procedure. Throughout the study, patients remained blinded. The researcher conducting evaluations was also blinded to group allocations, and the researcher administering the intervention was unaware of the assessment results, ensuring a double-blind study design.

2.5 Interventions

2.5.1 Standard treatment for xerostomia (PBM group and Placebo Group)

Patients received guidance from the principal researcher (PI) on proper oral hygiene, low-sugar diets, daily topical fluoride use, and antimicrobial mouth rinses for dental caries prevention, as well as, oral hydration. They were advised to avoid smoking and consuming caffeinated beverages. When necessary, measures, such as oral lubricants, artificial saliva, aspiration prevention, and careful fluid intake during meals were instituted. All study participants were also referred to outpatient clinics at the University for medical follow-up to control medications, underlying conditions, and clinical status. They are also supported by a nutritional follow-up team and dental total care.

2.5.2 PBM Intervention Group

In addition to the standard treatment described above, PBM therapy sessions were conducted twice a week for 6 consecutive weeks in one of the medical clinical offices at the University. Based on studies by Heiskanen and Hamblin [26], Golez et al. [27], Marashian et al. [28], Matos et al. [29], Sachet et al. [30], and Nemeth et al. [18], irradiation was performed transcutaneously on the cutaneous topography of the salivary glands using the Fluence Maxx HTM ™ device, covering an irradiation area of a LED cluster with 13.20 cm^2 (area of each LED 0.282cm^2). The method involves applying a red LED cluster to the topography of the three major pairs of salivary glands (1 application in parotid and 1 concurrent application in submandibular and sublingual for each side) extraorally. The parameters used are detailed in Table 1. Participants in the control group received the standard xerostomia treatment described above as well as placebo PBM to mask the treatment. The number of points, frequency, and location of the PBM application were the same as those described in the PBM

Intervention Group item, but the placebo PBM device was turned off. The noise when the device was activated was recorded and used to mimic the irradiation from a cell phone.

Table 1 - Description of the parameters used to perform PBM in patients diagnosed with xerostomia included in the study

Parameters	Values/Units
Wavelength (λ)	660 nm
Radiant power (P) of the device	3000 mW
Irradiance	227 mW/cm2
Mode	Continuous
Technique	Perpendicular
Exposure time per point (t)	09 sec
Energy Density	2 J/cm2
Energy per session	54 J each side, 108 J total
Radiant energy (E) per LED	4.5 J
Energy per cluster	27 J
Area irradiated in each session	13.20 cm2
Extraoral locations	parotid glands
	submandibular glands
	Sublingual glands
Number of sessions and frequency	twice a week for 6 weeks
Application technique	perpendicular 01 cm distance between applicator and skin

2.6 Outcomes and evaluations

The primary outcomes were improvements in the Oral Health Impact Profile (OHIP-14) [31] and the Xerostomia Inventory (XI) Scale [32].
Secondary outcomes were improvements on the Brazilian version of the SF-36 Quality of Life Scale [33], the Brazilian Version of Functional Independence Measure (FIM) [34], sialometry, and salivary pH.

A researcher blind to patient allocation carried out the pre-treatment assessment (on the same day as the application of the informed consent form and allocation into groups) and also the final assessment no later than 15 days after the last therapeutic session.

Epidemiological data were also collected from the medical records of the included patients: nutritional assessment and anthropometric measurements of body weight, height, and Body Mass Index (BMI) [35, 36] age, gender, underlying clinical conditions, medications used, previous vaccination against COVID-19 status to characterize the sample.

2.7 Statistical Analysis

Descriptive measures were obtained with the calculation of mean, standard deviation, median, and quartiles for groups and moments. To assess the normality of the data, the Shapiro-Wilk test was applied. For data with symmetrical (normal) distribution, a Student's t-mean comparison test was performed for groups fixing moments and a paired t-test for comparison between moments fixing groups. Data that did not present normality were represented as means and quartiles and the comparison for groups was made using the Mann-Witney test fixing moments and the Wilcoxon test for moments fixing groups. In all tests, the significance level was set at 5% or the corresponding p-value. All analyses were performed using SAS for Windows, v.9.4, and STATISTICA for Windows, v.10.

3. RESULTS AND DISCUSSION

A total of 10 patients (05 PBM group and 05 control group) agreed to take part in the study and the diagnoses of long COVID and xerostomia after COVID were confirmed in the initial assessment. There was no withdrawal of participants during the study. No adverse events were reported. In 02 patients (PBM group), it was not possible to keep the blinding of the researcher during the intervention, even though these 02 participants remained blind in relation to the therapeutic group allocation. Also in 02 patients (PBM group), it was also not possible to evaluate pre-treatment salivary pH. The clinical and epidemiological data collected from the medical records of the included patients are presented in Table 2.

Table 2 - Clinical and epidemiological data collected from the medical records of included patients.

Variables	**Values**
Age (years)	71.6 (mean)
Feminine	6 (60%)
Vaccinated*	3 (30%)
Type of service n (%)	
Outpatient	3 (30%)
Hospitalization	7 (70%)
Comorbidities n (%)	
Systemic Arterial Hypertension	7 (70%)
Dyslipidemia	5 (50%)
Diabetes Mellitus	4 (40%)
Chronic obstructive pulmonary disease	2 (20%)
Polypharmacy n (%)	4 (40%)
Nutritional status	
Low weight	2 (20%)
Eutrophy	6 (60%)
Overweight	0 (0%)
Obesity	2 (20%)

*: 2 doses + 2 boosters.

There were no statistically significant differences between the PBM and placebo groups in relation to the values of the FIM, SF-36, OHIP-14, XI, BMI, age, as well as sialometry or salivary pH evaluated in pre-intervention baseline moment, demonstrating homogeneity of the sample and groups. Also it was no significant differences between the PBM and placebo groups in the post-intervention moments for all evaluated outcomes (Tables 3, 4, and 5; Figures 1 and 2).

Table 3 - Comparison of the age, polipharmacy and BMI in the groups at the baseline.
Results should be clearly described in a concise manner. Results for different parameters should be described under subheadings or in separate paragraph. Table or figure numbers should be mentioned in parentheses for better understanding.

Table 3 - Comparison of the age, polipharmacy and BMI in the groups at the baseline

Variables	**Groups**	**Baseline mean (SD)**	**p value ***
Age	Photobiomodulation	66.2±4.54	0.061
	Placebo	77±10.14	
BMI	Photobiomodulation	27.25±4.54	0.317
	Placebo	24.32±4.15	
Polypharmacy	Photobiomodulation	2.6±2,40	0.07
	Placebo	3.0±1.87	

BMI Body Mass Index.

**p-values* refer to student's t-test

Table 4- The mean and standard deviation values of salivary pH, levels of non- stimulated and stimulated saliva in PBM and placebo groups at baseline and post-treatment moment

Variables	Groups	Baseline mean (SD)	Post-treatment mean (SD)	p value**
Salivary pH	PBM	7.1±0.36	7.3±0.47	0.245
	Placebo	7.0±0.24	6.9±0.50	0.736
	p value*	0.652	0.190	-
Unstimulated salivary flow	PBM	0.34±0.28	0.59±0.52	0.195
	Placebo	0.61±0.23	0.61±0.30	0.986
	p value*	0.136	0.931	-
Stimulated salivary flow	PBM	0.74±0.22	1.29±0.47	0.091
	Placebo	0.88±0.30	0.84±0.52	0.854
	p value*	0.414	0.189	-

**p-values* refer to student's t-test

***p-values* refer to paired t-test

significant different for p-value < 0.05

Table 5- The mean and standard deviation values of SF-36 Scale, OHIP-14, XI and FIM Scale in PBM and placebo groups at baseline and post-treatment moment

Variables	Groups	Mean (SD) Baseline (Q1 -Q3)	Mean (SD) Post-treatment (Q1 -Q3)	p value**
SF 36 (**)	PBM	89 (68-100)	97 (96-100)	0,617
	Placebo	98 (52-99)	94 (54-99)	0,371
	p valor	0,753	0,345	-
OHIP-14 (**)	PBM	22 (14-28)	12 (5-13)	0,371
	Placebo	16 (12-13)	22 (15-29)	0,371
	p valor	1,000	0,530	-
XI (**)	PBM	27 (18-38)	18 (15-20)	0,073
	Placebo	25 (20-32)	28 (16-29)	0,371
	p valor	0,834	0,463	-
FIM (**)	PBM	90 (72-121)	102 (72-120)	0,671
	Placebo	100(60-100)	108 (70-119)	0,073
	p valor	0,529	1,000	-

p-values refer to paired t-test

significant different for p-value < 0.05.

(**) Mann-Whitney test testing groups and Wilcoxon test testing moments

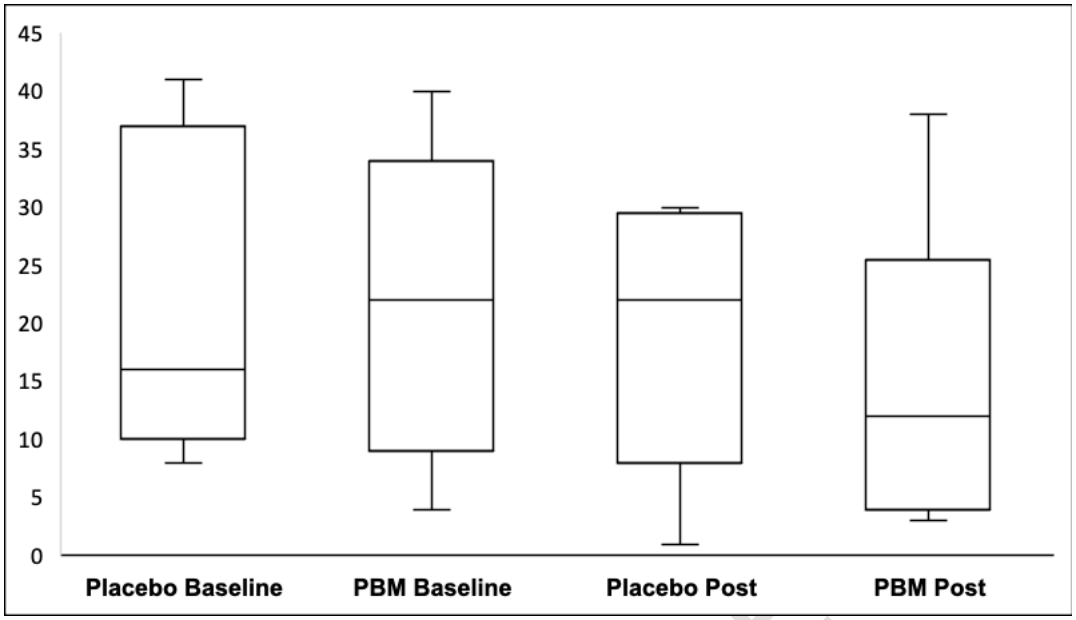

Figure 1: Box-plot graph values found the OHIP-14 questionnaire, comparing the baseline and post intervention moments in the placebo and PBM groups.

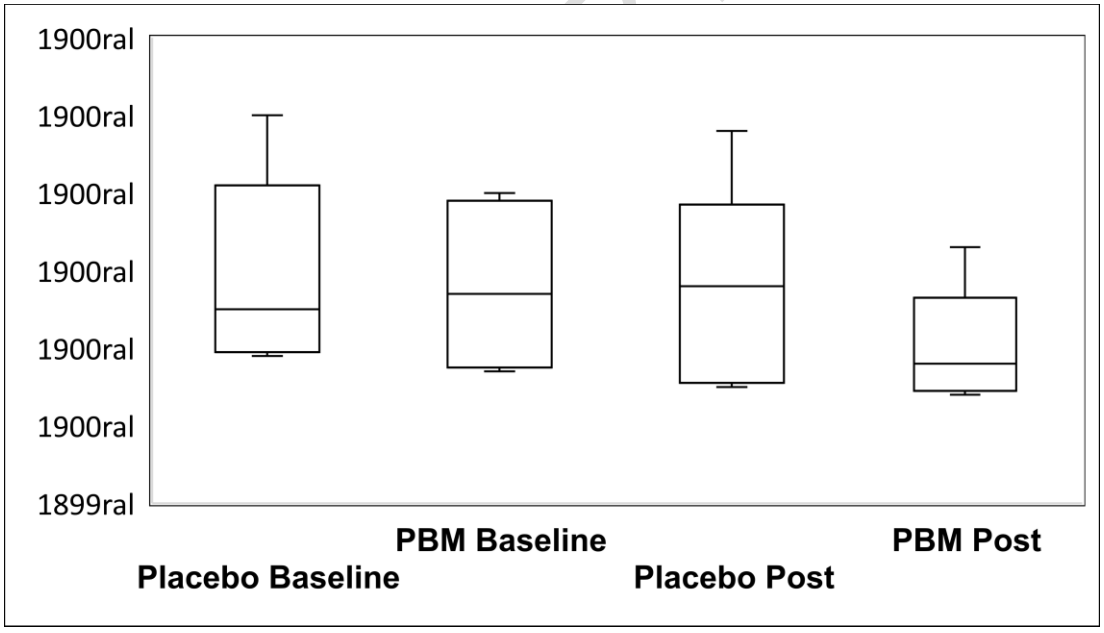

Figure 2: Box-plot graph values found the XI scale, comparing the baseline and post-intervention moments in the placebo and PBM groups.

In the individual analysis of the OHIP-14 items, it was found differences in the mean values of the PBM group for the question *"Was your diet impaired?"* (p 0.003) comparing the pre-intervention baseline moment with the post-intervention PBM moment. In parallel, in relation

to the XI items we found a difference in the mean values of the PBM group for the statement *"I get up at night to drink",* (p 0.008) and for the statement *"I have difficulty in eating dry foods",* (p 0.006), comparing the pre-intervention baseline moment with the post-intervention PBM moment in the PBM group not evident in the placebo group (Table 6 and 7).

Table 6: Values found in XI scale comparing the baseline and post-intervention moments in the placebo and PBM groups for each item individually

	Placebo mean (SD)			**PBM mean (SD)**		
	T1	T2	p value	T1	T2	p value
1-My mouth feel dry	2.2±1.30	1.8±1.48	0.662	2.4±1.67	2.8±1.09	0.668
2-I have difficulty in eating dry foods	2.0±0.70	2.2±1.09	0.741	2.8±0.83	1.0±0.70	**0.006***
3-I get up at night to drink	2.4±1.51	1.8±1.58	0.544	2.0±0.70	0.6±0.54	**0.008***
4-My mouth feels dry when eating a meal	2.2±0.83	1.8±1.30	0.582	2.0±1.22	1.4±1.14	0,445
5-I slip liquids to aid in swallowing food	2.6±1.14	1.6±1.34	0.240	2.2±1.48	0.4±0.54	0.050
6-I suck sweets or cough lollies to relieve dry mouth	1.6±1.34	2.6±1.14	0.240	2.4±0.84	1.2±1.30	0.133
7-I have difficulties swallowing certain foods	3.0±1.22	2.4±0.54	0.133	2.6±1.14	2.0±1.58	0.512
8-The skin of my face feels dry	1.8±2.04	1.4±1.67	0.744	1.8±1.48	1.6±1.14	0.817
9-My eyes feel dry	1.0±1.22	1.6±1.51	0.511	1.6±1.51	1.4±1.34	0.830
10-My lips feel dry	1.6±1.51	1.4±1.14	0.820	1.8±1.48	1.6±1.14	0.817
11-The inside of my nose feels dry	1.2±1.30	2.2±1.48	0.290	0,8±0.83	1,0±1,00	0.740

SD standard deviation, (XI) Xerostomia Inventory, (T1) Baseline, (T2) Post-treatment moment.

p-values refer to paired t-test.

*Significant different for p-value < 0.05 .

Table 7: Values found OHIP-14 questionnaire comparing the baseline and post-treatment moments in the placebo and PBM groups for each item individually

	Placebo mean (SD)			**PBM mean (SD)**		
	T1	T2	p value	T1	T2	p value
1 - Did you have trouble saying any words?	0.6±0.89	0.4±0.89	0.732	0.8±0.83	1.2±1.30	0.582
2 - Have you felt that the taste of food has gotten worse?	1.8±1.64	1.2±0.83	0.494	2.4±1.51	1.4±1.51	0.327
3 - Have you felt pain in your mouth or teeth?	1.2±1.09	1.2±0.83	1.000	1.6±1.67	1.2±0.83	0.649
4 - Did you feel uncomfortable eating any food?	2.2±1.64	1.4±0.89	0.374	2.8±1.64	2.2±1.30	0.541
5 - Were you worried?	0.8±0.83	0.8±0.83	1.000	0.6±0.89	0.6±1.34	1.000
6 - Did you feel nervous?	1.0±0.70	2.0±1.58	0.247	0.6±0.89	1.2±1.78	0.527
7 - Was your diet impaired?	2.2±1.30	2.6±1.14	0.619	3.2±1.09	1.4±1.14	**0.034***
8 - Did you have to stop eating?	2.2±1.30	0.8±0.83	0.084	2.8±1.64	1.4±1.67	0.218
9 - Did you find it difficult to relax?	2.0±1.41	1.4±1.67	0.557	1.4±1.94	1.4±1.94	1.000
10 - Were you embarrassed?	1.4±0.54	2.0±1.41	0.415	1.0±1.73	0.4±0.89	0.517
11 - Were you annoyed with people?	1.0±0.70	0.8±0.83	0.694	0.2±0.44	0.2±0.44	1.000
12 - Did you have difficulty doing your daily tasks?	1.6±0.89	1.2±0.83	0.486	0.8±1.87	0.4±0.89	0.670
13 - Did you feel that your life got worse?	2.0±1.87	1.8±1.48	0.856	2.2±1.78	1.0±1.00	0.236
14 - You can't do your daily tasks	2.0±1.87	1.8±1.48	0.856	1.2±1.78	0.2±0.44	0.285

*(SD) S*tandard Deviation, (OHIP-14) Oral Health Impact Profile-14, (T1) Baseline, (T2) Post-treatment moment.

p-values refer to paired t-test.

*Significant different for p-value < 0.05 .

3. DISCUSSION

This pilot study evaluated a group of patients with long COVID-19-associated xerostomia who were treated using an extraoral photobiomodulation protocol targeting the topography of the salivary glands. The pioneering study used standardized scales to assess outcomes such as the sensation of xerostomia, oral functionality, quality of life, salivary pH, and sialometry in a long COVID population.

COVID-19 infection has local and systemic effects on multiple organs, including the mouth and tongue [37, 38]. Although many studies have been published to evaluate the general impacts of these sequelae, oral manifestations are still underestimated and not well understood [8, 39]. Recently, a systematic review published by Gupta et al. [8] highlighted the high prevalence of oral manifestations among patients with COVID-19, particularly changes in taste (48%), followed by xerostomia (35%), oral ulceration (21%), hyperemia, and white lesions on the tongue and oral mucosa (2.4%). Interestingly, despite the high prevalence of xerostomia, concomitant salivary dysfunction was found in only 1.07% of cases, suggesting that the etiology of xerostomia in long COVID-19 is multifactorial.

Regarding the treatment of xerostomia, it is well-established that an interdisciplinary approach is primarily required. Although studies have already demonstrated that photobiomodulation is a promising technique for managing xerostomia of various etiologies, there are no studies evaluating its use specifically for xerostomia in long COVID. In this regard, this study is pioneering and has been designed by CONSORT guidelines.

In this study, we found a difference in the values of individual statements of the XI and OPHIP-14 scales when comparing baseline values with post-intervention values within the PBM group not observed in the placebo group. However, no significant differences were found between baseline and post-treatment values in the placebo group or the PBM group for any of the other outcomes evaluated. Additionally, there were no significant differences between the PBM and placebo groups in the post-intervention values for any evaluated outcomes. It is also important to highlight that, regarding the individual questions of the OHIP-14 and XI scales, the absolute values showed a tendency to improve during the treatment period for all groups. Specifically, the PBM group exhibited absolute values improvement in 9 statements of the OHIP-14 and 11 statements of the XI, while the placebo group showed improvement in 9 statements of the OHIP-14 and 10 statements of the XI. This suggests a tendency for improvement even in patients receiving a placebo, indicating that there may be some degree of spontaneous recovery in all cases.

Despite this, the total absolute values for stimulated salivary flow, FIM, OHIP-14 scales, and XI in the PBM group compared to the placebo group at the post-treatment moment are not statistically significant. The small sample size may have contributed to the lack of statistically significant differences in these values, despite the observed total numerical trend.

Regarding sample analysis, although there were no exclusion or inclusion criteria related to age, the mean age of the sample was over 60 years old, which reflects and may suggest that COVID xerostomia can be more likely in the elderly and frail population than in the young population, as well as other symptoms related to long COVID.

Finally, it is interesting to note that the values of stimulated salivary flow (averages of 0.74 ml/min in the PBM group and 0.88 ml/min in the placebo group) and non-stimulated salivary flow (averages of 0.34 ml/min in the PBM group and 0.61 ml/min in the placebo group) pre-intervention were found to be within the normal range [40, 41], suggesting that the pathophysiology of xerostomia in this population is not completely dependent on salivary volume and it may have influenced these negative results [7, 42, 43]. Other factors, such as inflammation of the taste buds, changes in the epithelium of the oral mucosa, or salivary biochemistry not studied in this project, may have a more determining role in xerostomia than the salivary volume itself. In fact, it has been highlighted for a long time the complexity of xerostomia and how factors such as quality of saliva, distribution of salivary flow, biochemical composition, fluid absorption, and evaporation, can impact xerostomia sensation[44–47].

In this context, intraoral PBM stimulation can be combined with extraoral methods to enhance symptom relief. Both intraoral and extraoral PBM of the salivary glands have distinct advantages and disadvantages. Intraoral irradiation offers precise targeting, less light dispersion, and easier access. However, it may cause discomfort or irritation to the mucosa during treatment, depending on the device and the patient's sensitivity. On the other hand, extraoral irradiation covers a broader area of the salivary glands, potentially leading to more effective stimulation of saliva production. It may also be less invasive and cause less discomfort compared to intraoral methods. However, extraoral irradiation might result in less precise targeting and greater scattering of therapeutic light. Therefore, the choice between these approaches should consider the individual needs and characteristics of each patient, as well as the desired outcome.

This pilot study has several limitations. The small sample size and short follow-up period may have negatively influenced the results, preventing the attainment of statistical significance for many of the evaluated outcomes. Additionally, while the scales used to assess oral functionality and quality of life are standardized and established, they remain subjective and prone to bias. Furthermore, the examiner was not blinded for two patients, and pH data was not collected for two cases, which affected the assessment of this outcome. It is also important to consider that factors not measured in this study, such as salivary biochemistry, other comorbidities that may influence or predispose patients to xerostomia, and mouth breathing, could have impacted the results. A more in-depth analysis, along with a thorough assessment of the clinical context, is essential for a comprehensive interpretation of these findings.

Despite these limitations, this study suggests that photobiomodulation may be a safe, and side-effect-free technique for adjuvant treatment of long COVID xerostomia.

4. CONCLUSION

This PBM protocol was not superior to placebo in treating long COVID xerostomia for the evaluated outcomes. However, it did show improvements in individual points of the OHIP-14 and XI scales, comparing pre-intervention values with post-intervention values within the PBM group. Nonetheless, it is important to emphasize the need for additional studies with larger sample sizes and longer follow-up periods to confirm and expand upon these results. Additionally, it is crucial to identify factors associated with dry mouth, such as oral breathing, and to evaluate saliva biochemistry. Considering associated extra and intraoral PBM irradiation of the salivary glands could be studied as a future approach to improving saliva production in patients with xerostomia due to long COVID.

COMPETING INTERESTS

THE AUTHORS HAVE NO RELEVANT FINANCIAL OR NON-FINANCIAL COMPETING OF INTERESTS TO DISCLOSE. THE AUTHOR(S) DECLARED NO POTENTIAL CONFLICTS OF INTEREST WITH RESPECT TO THE RESEARCH, AUTHORSHIP, AND/OR PUBLICATION OF THIS ARTICLE.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

This study meets the ethical guidelines for research and was approved by the Local University Research Ethics Committee under number 5.951.619 / Approval Number: CAAE 63694722.0.0000.5511 / 6.105.277. Participants were only included after obtaining proper consent and signing the Informed Consent Form (ICF). All patients received information regarding the study, its potential benefits and risks. All study procedures were explained in the

ICF signed by all participants prior to inclusion. All published data or data made available do not contain sensitive or patient-identifying information.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

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