IN VIVO STUDY OF THE APPLICATION OF PHOTOBIOMODULATION IN THE TREATMENT OF DYSGEUSIA IN PATIENTS POST COVID-19

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ABSTRACT: *Objective*: The aim of this study is to evaluate local and systemic photobiomodulation (PBM) in patients with COVID-19-related dysgeusia, with the expectation of improving taste dysfunction. *Background*: PBM has garnered attention as a potential therapy in long COVID, a condition characterized by many persistent symptoms following the acute phase of COVID-19. Among these symptoms, dysgeusia, or alt- ered taste perception, can significantly affect patients' quality of life. Emerging research suggests that PBM may hold promise in ameliorating dysgeusia by modulating cellular processes and reducing inflammation. Further clinical studies and randomized controlled trials are essential to establish the efficacy and safety of PBM for the treatment of dysgeusia in long COVID, but initial evidence suggests that this noninvasive modality may offer a novel avenue for symptom management. *Methods*: Seventy patients experiencing dysgeusia were randomly assigned to receive active local and systemic PBM (n = 34) or simulated PBM (n = 36). Low-power laser (red wavelength) was used at 18 spots on the lateral borders of the tongue (3 J per spot), salivary glands (parotid, sublingual, and submandibular glands—3 J per spot), and over the carotid artery for 10 min (60 J). Alongside laser therapy, all patients in both groups received weekly olfactory therapy for up to 8 weeks. *Results*: Dysgeusia improved in both groups. At weeks 7 and 8, improvement scores were significantly higher in the PBM group than in the sham group (p = 0.048). *Conclusions*: Combined local and systemic PBM, as applied in this study, proved effective and could serve as a viable treatment option for alleviating dysgeusia in long-COVID patients.
Clinical Trial Registration: RBR-2mfbkkk.
KEYWORDS: COVID-19, photobiomodulation, dysgeusia, low-level light therapy

SARS-CoV-2 was discovered in December 2019 and rap- idly became a global outbreak, with the disease being named COVID-19.[1] As research on COVID-19 has advanced, taste and smell disturbances have also been found to be common symptoms of the disease, especially in long COVID,[2] where these disorders can last for months or years and may recur over time.[3] In addition to the loss of smell and taste, chronic fatigue, shortness of breath, cognitive dysfunc- tion, memory issues, postexertional malaise, muscle pain/ spasms, sleep disorders, tachycardia/palpitations, cough, and chest pain are common in long COVID.[3]

Taste disturbances are classified as either quantitative or qualitative disorders, and dysgeusia is a qualitative distortion of taste.[4] However, this term is generally used to define any type of taste disorder.[5] This dysfunction can have several etiologies, including infectious diseases such as COVID-19.

Although its pathobiology remains unknown, SARS- CoV-2 may stimulate host antibody production, which can damage taste cells.[5] In addition, the presence of rhinorrhea, nasal congestion, and pharyngitis, which the disease can cause, may affect taste temporarily, or not, due to the resulting edema and inflammatory response.[5] Dysgeusia can also occur due to binding of SARS-CoV-2 to angiotensin- converting enzyme 2 (ACE2) present in several human organs and tissues, including the nervous system, epithelial cells of the tongue, and salivary glands.[6–9]

When ACE2 receptor cells become host to a virus, such as oral tissue cells, they can elicit an inflammatory res- ponse,[7,8,10] leading to impaired taste bud sensitivity and dysfunctional taste-related responses.[11] Another explanation for COVID-19-related dysgeusia is the spread of the virus through the bloodstream, which can reach the cribriform plate, thus coming into contact with the cerebral circulation and interacting with the cranial nerves.[5]

An important factor is patient reports of changes in appetite during the COVID-19 infection due to taste and smell disturbances. The presence of anorexia in patients infected with SARS-CoV-2 may lead to development of nutritional disorders in 3–56% of patients.[12–17] In addition, the senses of taste and smell are of paramount importance for quality of life as they provide protection against external hazards such as the identification of natural gas leaks, fire, and spoiled food and verification of personal hygiene.[18]

However, the diagnosis to confirm these sensations is imprecise and the degree of dysfunction that patients expe- rience is subjective.[18] A test that can be used to confirm and assess the degree of dysgeusia is gustometry.[5] According to Mueller et al.,[19] gustometry is a test in which drops con- taining different flavors at various concentrations can be applied to the tongue. Four major tastants at different con- centrations are dropped on the surface of the tongue: citric acid (sour), sucrose (sweet), sodium chloride (salty), and quinine (bitter).

The test results are recorded as any reduction in taste sensation in the areas where the different taste solutions have been applied. After confirming and evaluating the degree of dysgeusia, olfactory therapy may be appropriate to improve olfactory and gustatory dysfunction.[18,20]

A promising treatment to alleviate dysgeusia is the use of low-power lasers to perform local photobiomodulation (PBM) therapy.[21] Local and systemic PBM therapies have proven to be effective in improving dysgeusia resulting from other pathologies, without adverse effects on the pati- ent.[22–24] Furthermore, PBM therapy was used in other oral manifestations caused by long COVID, resulting in a posi- tive effect by improving sequelae, as demonstrated in the study by Pacheco et al.[25]

PBM is a noninvasive treatment that acts at the cellular level by increasing blood flow, oxygen consumption, aden- osine triphosphate (ATP) production, and antioxidant defenses.[26] Immunomodulatory effects may be achieved[27] mainly when local PBM is combined with systemic PBM, leading to increased immunity, induction of positive effects on the expression of immunoglobulins (IgA, IgM, and IgG), modulation of inflammation,[28] tissue regeneration,[29–31] and healing effects.[24]

PBM can also assist in the nerve regeneration pro- cess,[32,33] contributing to a reduction in the inflammatory process caused by binding of a virus to ACE2, mainly in the recovery of the cranial nerves affected by the infection. Therefore, systemic PBM may be indicated in the treat- ment of several pathogens, such as those causing infectious diseases.[34]

Knowledge of how to treat symptoms of COVID-19 is of paramount importance. Even though the disease has been largely mitigated and its variants have often spared olfactory and gustatory function,[35] several patients still experience dysgeusia and anosmia as consequences that adversely affect their quality of life. Therefore, offering therapeutic options to alleviate the sequelae of COVID-19 is important. The current study aimed to evaluate local and systemic PBM versus no PBM therapy in patients with COVID-19- related dysgeusia, with the expectation of improving taste dysfunction.

MATERIALS AND METHODS

This trial was conducted following the CONSORT guidelines.

A randomized, superiority, single-blind (participants), placebo-controlled parallel-group trial was designed to eval- uate the application of local and systemic PBM to reduce dysgeusia symptoms in long COVID. The trial was appro- ved by the Research Ethics Committee of Pontifícia Uni- versidade Católica de Campinas (PUC-Campinas) (protocol number: 5.301.778, approval number: 52441621.1.0000.5481) and registered in the Brazilian Clinical Trials Reg- istry (ReBEC) platform.

A random sample of 70 patients, recruited from May to December 2022, underwent local and systemic PBM with low-power laser at PUC-Campinas Dental Clinics.

The primary outcome was the effectiveness of local and systemic PBM in improving dysgeusia. The secondary out- come was time to improvement for each patient. Both out-comes were assessed using qualitative questionnaires. All patients received treatment and were followed up once a week for up to 8 weeks.

Eighty-five patients were initially screened. According to Legouté et al.,[36] considering an error of 20% (power of 80%), the observed effect size of 0.75, and two-sided ana- lyses, we calculated that a sample size of at least 30 patients per group was necessary. Sample size was calculated using G*Power statistical software, version 3.1.9.4 (Heinrich- Heine, Universita¨t Du¨sseldorf, Du¨sseldorf, Germany). Therefore, in this study, 34 patients received active PBM (PBM group), whereas 36 patients received simulated irra- diation (sham group).

Eligible participants were all patients aged 18 years or over, with a positive COVID-19 reverse transcription– polymerase chain reaction test associated with dysgeusia and who were no longer in the stage of disease transmission (15 days after the beginning of the study), had dysgeusia confirmed by a qualitative test, had satisfactory oral health status according to the decayed–missing–filled teeth index and periodontal charts, and agreed to participate in the study by signing an informed consent form. Exclusion criteria were pregnancy or lactation, not meeting the eligibility cri- teria, and nonattendance at follow-up visits.

The 70 patients included in the study were random- ized using a sequence generated through an internet-based randomization website (www.sealedenvelope.com) and allocated to each arm of the trial before history taking, as shown in the flow diagram (Fig. 1).

All patients were subjected to history taking (authors' own questionnaire), with collection of data such as sex, age, time since COVID-19 diagnosis, and the level of dissatis- faction with dysgeusia. In addition, qualitative question- naires for assessment of the degree of dysgeusia after taste testing and other yes/no questionnaires developed by the authors were also administered.

The degree of dysgeusia was assessed by asking patients to identify the taste felt in the drop of the test solution, consisting of the following tastants: sodium chloride (salty), sucrose (sweet), citric acid (sour), and quinine (bitter).[19] The answers should indicate the substance felt and taste inten- sity. The order the taste solutions were administered chan- ged every week, and patients were blinded to the taste solution used to avoid response bias.

The administrator of the taste solution was also blinded to the flavors applied. Subsequently, a yes/no questionnaire was administered to assess food items and products consumed daily by the patients. Both questionnaires were administered weekly to assess the progress of each patient in the treatment.

After completing the questionnaires, patients received treatment according to group assignment. Before PBM, the oral cavity was cleaned with 0.12% chlorhexidine (Riohex Gard; Rioquímica S/A, São José do Rio Preto, SP, Brazil) using sterile gauze in all participants.

PBM group

Participants received local irradiation with active light from a low-power laser unit (Therapy EC; DMC, São Car- los, SP, Brazil), with the aid of a spacer, operated at energy of 3 J per spot,[37–39] energy density of 30.61 J/cm^2, wave- length of 660 nm, power of 100 mW/cm^2, and output spot of 0.098 cm^2 for 30 sec, in continuous wave mode.[23,24,38] Local PBM was performed at 18 spots on the lateral borders of the tongue, which correspond to the taste buds (Fig. 2), and also in the salivary glands bilaterally (parotid, sublingual, and submandibular glands).

Using the same laser equipment, with a 600-lm optical fiber and the same spacer, patients also received systemic irradiation over the carotid artery with the laser unit operated at 60 J of energy for 10 min while wearing a neck collar for neck irradiation (Fig. 3).[24] In addition, patients received guidance on olfactory therapy that involved sniffing sub- stances such as lemon, rose, eucalyptus, and cloves for 20 sec each, twice a day, for 2 months (protocol adapted from Whitcroft and Hummel).[40]

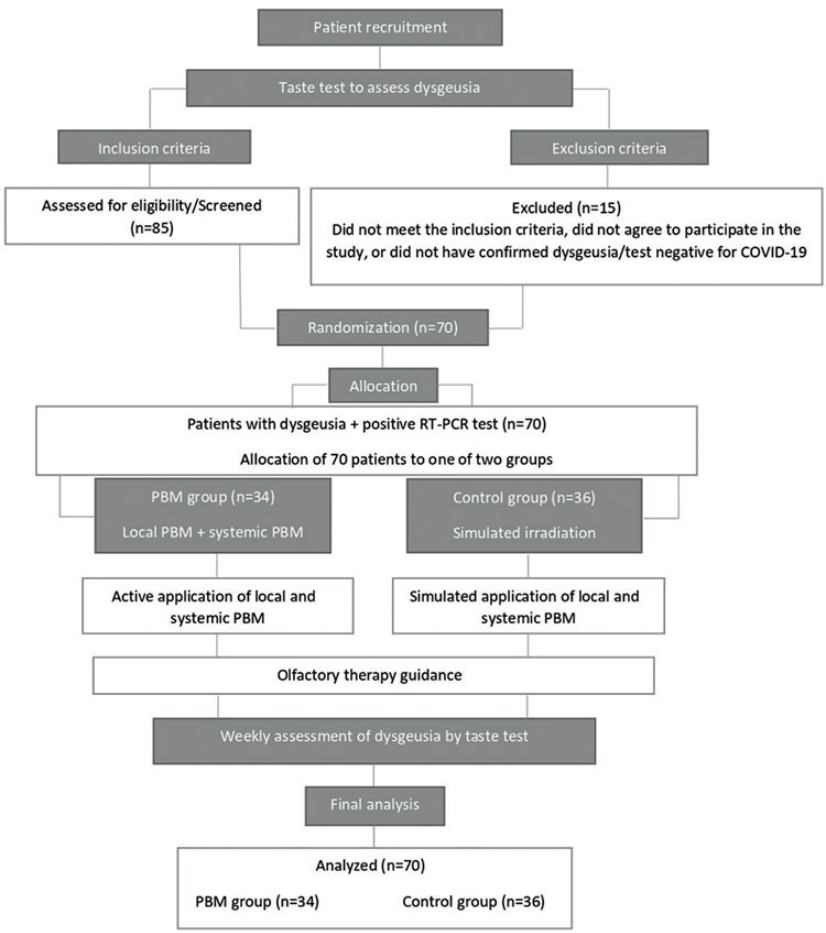

FIG. 1. CONSORT flow diagram.

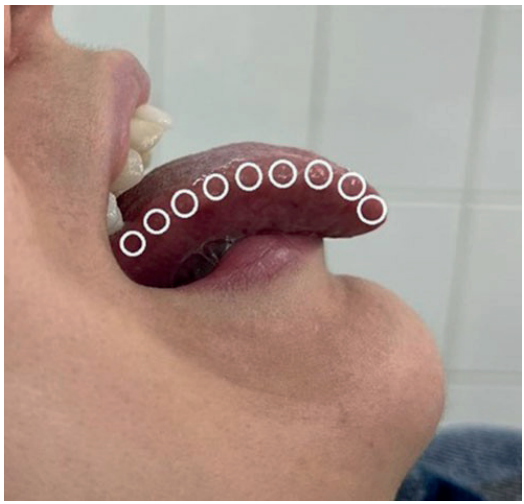

FIG. 2. Irradiation spots on the lateral borders of the tongue, corresponding to the taste buds.

FIG. 3. Application of systemic PBM on the carotid artery. PBM, photobiomodulation.

Sham group

Participants received simulated local and systemic app- lication of PBM on the same spots/artery irradiated in the PBM group, with the laser unit emitting sounds, but with the light not activated. Because the participants were wearing dark laser safety glasses during application and the appli- cation sites were not visible to the participant (intraoral spots and carotid artery), they could not see whether or not the light was on. Participants in the sham group received the same guidance on olfactory therapy provided to the PBM group.

The results were tested for normality of distribution using the Shapiro–Wilk test, and those with normal distribution were analyzed by Student's *t* test. Those with nonparametric distribution were analyzed using the Mann–Whitney *U* test. Subsequently, the size of the differences was estimated using Cliff's delta effect size, group similarities were ass- essed using the chi-square test, and the effect size was assessed using odds ratio. The significance level was set at 5% for all analyses.

RESULTS

Of 70 study participants, 16 were men (22.90%) and 54 were women (77.10%). Overall, mean patient age was 44.57 (standard deviation, 13.80) years. The number of partici- pants assessed weekly per group is shown in Table 1.

According to information obtained during history taking, 56 patients were diagnosed with COVID-19 only once, fol- lowed by 12 patients who tested positive for the virus twice, and only 1 patient who was diagnosed three times.

At weeks 7 and 8, there were more clinical discharges in the PBM group, with a dysgeusia reversal rate of 32.35% (vs. 13.80% in the sham group).

The two groups did not differ significantly in terms of sample characterization variables ($p > 0.05$) (Table 2), thus being comparable for the outcomes of interest.

Time to reversal of dysgeusia is shown in Table 3. The medians were similar, but the distributions were statistically different ($p < 0.05$), with a shorter reversal time at the 25th percentile for the PBM group. Regarding total gustometry,

the PBM group obtained higher scores than the sham group at week 8. For sour, scores were higher in the PBM group at weeks 7 and 8; for sweet, scores were higher in the PBM group at week 8; for salty, there was no difference between the PBM and sham groups in any of the assessment weeks; and for bitter, scores were higher in the PBM group at week 8.

	Group	
Week	*Sham*	*PBM*
1	36	34
2	36	34
3	36	34
4	36	33
5	36	32
6	34	30
7	33	27
8	31	23

Table 1. Number of Participants Assessed Over the Weeks per Study Group

PBM, photobiomodulation.

TABLE 2. DISTRIBUTION OF THE SAMPLE IN THE STUDY GROUPS ACCORDING TO SEX, AGE, AND TIME SINCE COVID-19 DIAGNOSIS AND COMPARISON OF THESE VARIABLES BETWEEN THE STUDY GROUPS

	Group		
Variable	*Sham*	*PBM*	p
Sex, *n* (%)			
Male	6 (37.50)	10 (62.50)	0.260[a]
Female	30 (55.60)	24 (44.40)	
Age (years), mean (SD)	45.86 (±13.06)	43.21 (±14.62)	0.425[b]
Time since COVID-19 diagnosis, mean (SD)	17.36 (±8.30)	16.12 (±8.51)	0.538[b]

[a]Pearson's chi-square test.
[b]Student's *t* test.
SD, standard deviation.

TABLE 3. COMPARISON BETWEEN STUDY GROUPS FOR TOTAL, SOUR, SWEET, SALTY, AND BITTER GUSTOMETRY OVER THE STUDY ASSESSMENT WEEKS

		Group			
Variable	*Week*	*Sham Median (p25; p75)*	*PBM Median (p25; p75)*	p[a]	*ES*
Time to reversal		8.00 (8,00; 8.00)	8.00 (7.00; 8.00)	0.048	0.18 (small)
Gustometry—total	1	4.00 (3.00; 4.75)^{A}	4.00 (3.00; 5.00)^{A}	0.724	0.04 (very small)
	2	4.00 (3.00; 5.00)^{A}	4.00 (3.00; 5.00)^{A}	0.937	0.01 (very small)
	3	5.00 (3.00; 5.00)^{AB}	4.50 (4.00; 5.00)^{AB}	0.990	0.00 (very small)
	4	5.00 (4.00; 6.00)^{AB}	4.00 (4.00; 6.00)^{AB}	0.520	0.11 (very small)
	5	5.00 (4.00; 6.00)^{AB}	5.00 (5.00; 6.00)^{AB}	0.285	0.07 (very small)
	6	5.00 (4.00; 6.00)^{AB}	6.00 (4.00; 6.00)^{B}	0.130	0.01 (very small)
	7	5.00 (4.00; 6.50)^{B}	6.00 (5.00; 7.00)^{BC}	0.123	0.10 (very small)
	8	5.00 (4.00; 7.00)^{C}	7.00 (6.00; 8.00)^{C}	<0.001	0.09 (very small)
Gustometry—sour	1	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.836	0.02 (very small)
	2	1.00 (1.00; 1.00)^{A}	1.00 (1.00; 1.00)^{A}	0.810	0.02 (very small)
	3	1.00 (1.00; 1.00)^{A}	1.00 (1.00; 1.00)^{A}	0.308	0.10 (very small)
	4	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.091	0.17 (small)
	5	1.00 (1.00; 2.00)^{A}	1.50 (1.00; 1.00)^{AB}	0.238	0.08 (very small)
	6	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.719	0.18 (small)
	7	1.00 (1.00; 1.50)^{A}	1.00 (1.00; 2.00)^{A}	0.044	0.08 (very small)
	8	1.00 (1.00; 2.00)^{A}	2.00 (2.00; 2.00)^{B}	<0.001	0.12 (very small)
Gustometry—sweet	1	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.500	0.07 (very small)
	2	1.00 (1.00; 1.00)^{A}	1.00 (1.00; 2.00)^{A}	0.578	0.06 (very small)
	3	1.00 (1.00; 2.00)^{A}	1.00 (1.50; 2.00)^{A}	0.202	0.15 (small)
	4	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.937	0.08 (very small)
	5	1.00 (1.00; 2.00)^{A}	1.50 (1.00; 2.00)^{AB}	0.251	0.07 (very small)
	6	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.347	0.12 (very small)
	7	2.00 (1.00; 2.00)^{B}	1.00 (1.00; 2.00)^{A}	0.589	0.32 (small)
	8	1.00 (1.00; 2.00)^{A}	2.00 (1.00; 2.00)^{B}	0.046	0.25 (small)
Gustometry—salty	1	1.00 (1.00; 1.00)^{A}	1.00 (1.00; 1.00)	0.350	0.11 (very small)
	2	1.00 (1.00; 1.00)^{A}	1.00 (1.00; 2.00)^{A}	0.782	0.03 (very small)
	3	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 1.00)^{A}	0.193	0.15 (very small)
	4	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.201	0.18 (very small)
	5	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.263	0.18 (very small)
	6	1.00 (1.00; 2.00)^{A}	1.00 (1.00; 2.00)^{A}	0.425	0.13 (very small)
	7	1.00 (1.00; 2.00)^{A}	2.00 (1.00; 2.00)^{B}	0.240	0.15 (very small)
	8	1.00 (1.00; 2.00)^{A}	2.00 (1.00; 2.00)^{B}	0.152	0.30 (small)
Gustometry—bitter	1	0.00 (0.00; 1.00)^{A}	0.50 (0.00; 1.00)^{A}	0.578	0.06 (very small)
	2	1.00 (0.00; 1.00)^{A}	1.00 (0.00; 1.00)^{A}	0.532	0.07 (very small)
	3	1.00 (0.00; 1.00)^{A}	1.00 (0.00; 1.00)^{A}	0.959	0.00 (very small)
	4	1.00 (0.00; 1.00)^{A}	1.00 (0.00; 1.00)^{A}	0.183	0.19 (small)
	5	1.00 (1.00; 1.00)^{AB}	1.00 (1.00; 2.00)^{B}	0.249	0.07 (very small)
	6	1.00 (1.00; 1.00)^{AB}	1.00 (1.00; 2.00)^{B}	0.074	0.02 (very small)
	7	1.00 (1.00; 2.00)^{B}	2.00 (1.00; 2.00)^{B}	0.128	0.12 (very small)
	8	1.00 (1.00; 2.00)^{B}	2.00 (2.00; 2.00)^{B}	0.002	0.16 (small)

Different uppercase letters in the same column for the same gustometry group in each of the study groups indicate statistically significant differences between the assessment weeks.
[a]Mann–Whitney *U* test. Level of significance = 5%.
ES, effect size (Cliff's delta).

After exposure of the PBM and sham groups to the same stimuli or when asked about the influence of situations/ exposures on taste, there was a statistically significant dif- ference between the groups at weeks 3 and 8 ($p < 0.05$), where PBM improved the participants' taste by 1.33 and

1.26 times, respectively (Table 4). These results indicate that PBM improved participants' dysgeusia compared with sham irradiation. According to the evaluated parameters, the current study has an inference power of above 83%.

Figure 4 shows a graphic representation of the distribu- tion of total gustometry scores over the assessment weeks. Weeks 7 and 8 showed differential rates in the PBM group, as patients who received PBM had a higher rate of imp- rovement within the proposed time period than those in the sham group.

TABLE 4. COMPARISON BETWEEN STUDY GROUPS FOR QUALITY OF TOTAL GUSTOMETRY (FOR ALL FOODS—$n=8$; FOOD CONSISTENCY AND SMELL—$n=6$; AND SITUATIONS/EXPOSURES—$n=4$) IN EACH OF THE STUDY ASSESSMENT WEEKS

		Gustometry			
Week	*Group*	*Abnormal* n *(%)*	*Normal* n *(%)*	*p*[a]	*ES*
1	PBM	688 (72.30)	264 (27.70)	0.343	1.07 (medium)
	Sham	708 (70.20)	300 (29.80)		
2	PBM	618 (64.90)	334 (35.10)	0.537	0.94 (small)
	Sham	668 (66.30)	340 (33.70)		
3	PBM	528 (55.50)	424 (44.50)	0.003	0.75 (small)
	Sham	627 (62.20)	381 (37.80)		
4	PBM	485 (52.50)	439 (47.50)	0.784	0.97 (small)
	Sham	536 (53.20)	472 (46.80)		
5	PBM	371 (41.4)	525 (58.60)	0.194	0.88 (small)
	Sham	448 (44.40)	560 (55.60)		
6	PBM	334 (41.10)	478 (58.90)	0.498	0.93 (small)
	Sham	407 (42.80)	545 (57.20)		
7	PBM	283 (37.40)	473 (62.60)	0.317	0.90 (small)
	Sham	380 (39.90)	572 (60.10)		
8	PBM	197 (30.60)	447 (69.40)	0.038	0.79 (small)
	Sham	320 (35.70)	576 (64.30)		

[a]Pearson's chi-square test. Level of significance = 5%.
ES, effect size (odds ratio).

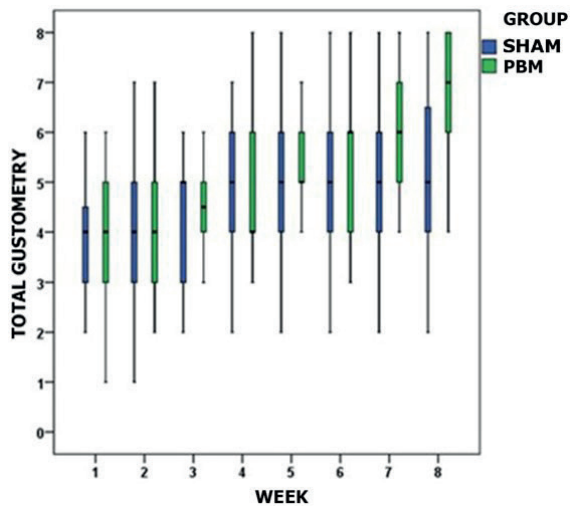

FIG. 4. Graphic representation of the distribu- tion of total gustometry scores over the assessment weeks per study group

DISCUSSION

Dysgeusia is a symptom commonly reported by people who have had COVID-19. Among hospitalized and non- hospitalized patients with COVID-19, with consequent taste disorders, 46% reported ageusia[41] and 44% had some type of gustatory dysfunction.[42] Taste disorders can affect appetite during and after the disease incubation period, leading to the development of nutritional disorders[12–17] due to altered food taste and lack of pleasure from eating. In this context, mainly due to reduced quality of life in these patients,[43] studies have investigated possible treat- ments to effectively improve COVID-19-induced taste dysfunction.[44–48]

Given the lack of scientific evidence of protocols developed for COVID-19-related dysgeusia, this study evaluated combined local and systemic PBM to treat patients with dysgeusia after SARS-CoV-2 infection, with the expecta- tion of improving taste dysfunction. According to Pacheco et al.,[25] the use of PBM in oral manifestations caused by long COVID, such as herpetic lesions, aphthous stomatitis, and other ulcerative lesions, yielded positive results, leading to improvement in tissue repair and patients' quality of life. In systemic PBM, the carotid artery was chosen for the procedure due to the triggering of a homeostatic hormonal balance, greater vascularization of the anterior region of the face,25 and because of proximity to the local PBM irradiation spots. Taste tests were used to reduce the subjectivity of patients' responses to the degree of dysgeusia. This test was initially proposed by Mueller et al.,19 and later used by Borah et al.,44 Ghods and Alaee,47 and Thomas et al.,43 for application of solutions containing substances that stimulate the four main taste senses (sweet, sour, bitter, and salty), in which the patient should identify the flavor applied. In this study, taste tests were applied once a week to assess patients' weekly progress.

In addition to taste testing, Singh et al.48 and Thomas et al.43 also proposed asking simple questions with yes/no answers. Given the lack of validated questionnaires in the literature for this purpose, the present authors developed questions about commonly consumed food items and products, in which the answers were ''yes'' for any taste abnormality and ''no'' for normal taste perception of that food item or product. Therefore, development of the questionnaires was intended to further reduce the subjectivity of taste sensations reported by the patients.

Given the lack of validated questionnaires in the literature that could measure the degree of dysgeusia and patients' progress throughout treatment with PBM in these cases, the present authors developed questions intended to reduce subjectivity in the answers provided by the patients, following the reports by Mueller et al.,19 Borah et al.,44 Ghods and Alaee,47 Thomas et al.,43 and Singh et al.,49 who proposed simple questionnaires with yes/no answers, but did not mention a validated questionnaire in the literature. Therefore, the questions developed by the present authors are not validated, being administered for the first time in this study. Even if there were qualitative questionnaires to be administered to patients, there could still be variation in patients' perception of taste and smell. Therefore, these factors can be interpreted as a weakness of the study alongside the nonvalidation of the questionnaires, requiring further research to refine this type of investigation.

In view of the physiology of the human body, distorted taste perception is often accompanied by an altered sense of smell.4,43,50,51 Anosmia is not always followed by dysgeusia, but in most cases, dysgeusia is followed by anosmia. Therefore, in addition to PBM, the patients in our study also received olfactory training. According to Borah et al.,44 Ghods and Alaee,47 Thomas et al.,43 and Singh et al.48 within the context of long-COVID symptoms and according to Whitcroft and Hummel40 for other olfactory disorders, olfactory training involves sniffing of easily accessible substances that do not cause nasal obstruction.

The protocol used in this study was adapted from the study by Whitcroft and Hummel40 as it facilitates patients' adherence to training and agrees with reports from the literature. In the present study, the dysgeusia assessment instrument was developed with therapeutic goals similar to those of Pacheco et al.23 in the treatment of oral mucositis due to the lack of studies in the literature for this purpose. Our sample consisted of 54 women and 16 men. According to Thomas et al.,43 women have a greater ability to perceive taste, that is, they can more easily perceive whether a taste is normal or abnormal. However, although there was a discrepant number of men and women in our study sample, there was no statistically significant difference between the groups ($p = 0.260$). Time to reversal of dysgeusia had similar medians in the PBM and sham groups. There were cases of 100% improvement of dysgeusia in both groups. However, in the sham group, only 13.80% of patients achieved complete reversal of dysgeusia, whereas in the PBM group, the complete reversal rate was 32.25%. Furthermore, substantial improvement was noted in a shorter time period in patients who had long COVID for a longer time in the PBM group compared with the sham group, in which the patient profile was the same, but such improvement took longer to occur. All patients included in this study received some type of treatment: either the actual application of local and systemic PBM plus olfactory therapy or the placebo effect of local and systemic PBM plus olfactory therapy. It should be noted that the purpose of the present study was to demonstrate a comparative effect between treatment arms to determine whether PBM therapy would be effective or not in reversing dysgeusia, as it proved to be in the study by Pacheco et al.,23 who showed an improvement in taste disturbance symptoms in cancer patients. The present study included patients at different stages of COVID-19 and with other underlying conditions, which can be considered a limitation of the study. Even though efforts were made to standardize participant recruitment, including sex, age, and time since COVID-19 diagnosis, we were unable to cover all the different stages of the disease and its other underlying conditions.

PBM can exert a two-phase effect: in the first phase, the effect is immediate and occurs by direct irradiation of cellular components, and in the second phase, a delayed response occurs (after hours or days). These mechanisms of action result from activation of endogenous chromophores and light absorption by water present in cells and by various mediators such as growth factors, pro- and anti-inflammatory cytokines, metalloproteinases, and molecules such as ATP and reactive oxygen species. Mediators stimulate cell

proliferation, angiogenesis, and immune responses, modulating apoptosis and improving cell survival.26,29 As a result, PBM is an effective treatment indicated for the repair and maintenance of oral tissues, which may include cases of dysgeusia in which several lesions occur mainly in the cranial nerves and taste buds. Weeks 7 and 8 were crucial for differentiating the results between the groups since the number of discharges was higher in the PBM group in these weeks, that is, the PBM group produced better results than the sham group. PBM therapy, in addition to restoring the normal functioning of cells and oral tissues, is a nonthermal,52 noninvasive,53 and nondrug48 curative treatment option for dysgeusia, unlike previously proposed treatments with medications, with vitamin supplementation, or with medications combined with vitamin supplementation.44–48

In addition to the present study, the systematic review conducted by Pacheco et al.25 showed that PBM is an effective therapy to treat oral lesions as sequelae of COVID-19, whether alone or combined with another therapy such as antimicrobial photodynamic therapy (aPDT). Therapies with these alternatives are low cost and easy to use in offices and hospitals and have proven effective in repairing oral manifestations in long COVID.25 In the present study, PBM alone was sufficient to produce a positive result in reversing symptoms, eliminating the need to combine it with aPDT, as the patients in our sample did not have oral infections. However, due to the paucity of randomized controlled trials focused on long COVID, particularly on restoring taste sensation, further research is needed to establish a protocol for the treatment of each post-COVID-19 sequela. The present authors also suggest that further studies with a longer follow-up period should be conducted to measure remission of dysgeusia in more detail.

CONCLUSIONS

The combined approach of local and systemic PBM, as applied in this study, was found to be effective and could serve as a viable treatment option for alleviating dysgeusia in patients with long COVID.

REFERENCES

1. Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. Biomed J 2020; 43(4):328–333; doi: 10.1016/j.bj.2020.04.007.

2. Cecchini MP, Brozzetti L, Cardobi N, et al. Persistent chemosensory dysfunction in a young patient with mild COVID-19 with partial recovery 15months after the onset. Neurol Sci 2022;43(1):99–104; doi: 10.1007/s10072-021- 05635-y.

3. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022;22(4):e102–e107; doi: 10.1016/S1473- 3099(21)00703-9.

4. Maheswaran T, Abikshyeet P, Sitra G, et al. Gustatory dysfunction. J Pharm Bioallied Sci 2014;6(Suppl. 1):S30– S33; doi: 10.4103/0975-7406.137257.

5. Barasch A, Epstein J. Avaliac¸ão de distu´rbios do paladar. bAU5 BMJ Best Practice, London. Available from: https://best practice.bmj.com/topics/pt-br/971/pdf.pdf

6. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26(5):681– 687; doi: 10.1038/s41591-020-0868-6.

7. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12(1):8; doi: 10.1038/s41368- 020-0074-x.

8. Xu J, Li Y, Gan F, et al. Salivary glands: Potential reservoirs for COVID-19 asymptomatic infection. J Dent Res 2020;99(8):989; doi: 10.1177/0022034520918518.

9. Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019- nCoV infection. Front Med 2020;14(2):185–192; doi: 10 .1007/s11684-020-0754-0.

10. Wang L, Gillis-Smith S, Peng Y, et al. The coding of valence and identity in the mammalian taste system. Nature 2018;558(7708):127–131; doi: 10.1038/s41586-018-0165-4.

11. Mariz BALA, Brandão TB, Ribeiro ACP, et al. New insights for the pathogenesis of COVID-19-related dysgeusia. J Dent Res 2020;99(10):1206; doi: 10.1177/ 0022034520936638.

12. Carignan A, Valiquette L, Grenier C, et al. Anosmia and dysgeusia associated with SARS-CoV-2 infection: An agematched case-control study. CMAJ 2020;192(26):E702– E707; doi: 10.1503/cmaj.200869.

13. Kosugi EM, Lavinsky J, Romano FR, et al. Incomplete and late recovery of sudden olfactory dysfunction in COVID-19. Braz J Otorhinolaryngol 2020;86(4):490–496; doi: 10.1016/j.bjorl.2020.05.001.

14. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683–690; doi: 10 .1001/jamaneurol.2020.1127.

15. Moein ST, Hashemian SM, Mansourafshar B, et al. Smell dysfunction: A biomarker for COVID-19. Int Forum Allergy Rhinol 2020;10(8):944–950; doi: 10.1002/alr.22587.

16. Spinato G, Fabbris C, Polesel J, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARSCoV- 2 infection. JAMA 2020;323(20):2089–2090; doi: 10 .1001/jama.2020.6771.

17. Zahra SA, Iddawela S, Pillai K, et al. Can symptoms of anosmia and dysgeusia be diagnostic for COVID-19? Brain Behav 2020;10(11):e01839; doi: 10.1002/brb3.1839.

18. Doty RL. Treatments for smell and taste disorders: A critical review. Handb Clin Neurol 2019;164:455–479; doi: 10.1016/B978-0-444-63855-7.00025-3.

19. Mueller C, Kallert S, Renner B, et al. Quantitative assessment of gustatory function in a clinical context using impregnated ‘‘taste strips’’. Rhinology 2003;41(1):2–6.

20. Kronenbuerger M, Pilgramm M. Olfactory training. In: StatPearls [Internet]. StatPearls Publishing: Treasure Island, FL, USA; 2023.

21. Bensadoun RJ, Nair RG. Low-level laser therapy in the management of mucositis and dermatitis induced by cancer therapy. Photomed Laser Surg 2015;33(10):487–491. doi: 10.1089/pho.2015.4022.

22. Mobadder ME, Farhat F, Mobadder WE, et al. Photobiomodulation therapy in the treatment of oral mucositis, dysgeusia and oral dryness as side-effects of head and neck radiotherapy in a cancer patient: A case report. Dent J (Basel) 2018;6(4):64; doi: 10.3390/dj6040064.

23. Pacheco JA, Schapochnik A, de Sá CC. Successful management of dysgeusia by photobiomodulation (PBM) in a cancer patient. Med Case Rep J 2019;2:114; doi: 10.31531/ 2581-5563.1000114.

24. Pacheco JA, Schapochnik A, de Sá CC, et al. Applied transdérmic photobiomodulator therapy about the primary carotide artery in patients under hormonal blockers and dynude disorders and pathogenic flora of orofaringeo and systemic repercussions. Am J Biomed Sci Res 2019;4(4): 271–278; doi: 10.34297/ AJBSR.2019.04.000813.

25. Pacheco JA, Molena KF, Martins CROG, et al. Photobiomodulation (PBMT) and antimicrobial photodynamic therapy (aPDT) in oral manifestations of patients infected by Sars-CoV-2: Systematic review and meta-analysis. Bull Natl Res Cent 2022;46(1):140; doi: 10.1186/s42269-022- 00830-z.

26. Pinheiro SL, Bonadiman AC, Borges Lemos ALDA, et al. Photobiomodulation therapy in cancer patients with mucositis: A clinical evaluation. Photobiomodul Photomed Laser Surg 2019;37(3):142–150; doi: 10.1089/photob.2018 .4526.

27. Farivar S, Malekshahabi T, Shiari R. Biological effects of low level laser therapy. J Lasers Med Sci 2014;5(2): 58–62.

28. de Matos BTL, Buchaim DV, Pomini KT, et al. Photobiomodulation therapy as a possible new approach in COVID-19: A systematic review. Life (Basel) 2021;11(6): 580; doi: 10.3390/life11060580.

29. Pires Marques EC, Piccolo Lopes F, Nascimento IC, et al. Photobiomodulation and photodynamic therapy for the treatment of oral mucositis in patients with cancer. Photodiagnosis Photodyn Ther 2020;29:101621; doi: 10.1016/j .pdpdt.2019.101621.

30. Tsai SR, Hamblin MR. Biological effects and medical applications of infrared radiation. J Photochem Photobiol B 2017;170:197–207; doi: 10.1016/j.jphotobiol.2017.04.014.

31. Hamblin MR, Nelson ST, Strahan JR. Photobiomodulation and cancer: What is the truth? Photomed Laser Surg 2018; 36(5):241–245. doi: 10.1089/pho.2017.4401.

32. Buchaim DV, Andreo JC, Ferreira Junior RS, et al. Efficacy of laser photobiomodulation on morphological and functional repair of the facial nerve. Photomed Laser Surg 2017;35(8):442–449; doi: 10.1089/pho.2016.4204.

33. Buchaim RL, Andreo JC, Barraviera B, et al. Effect of lowlevel laser therapy (LLLT) on peripheral nerve regeneration using fibrin glue derived from snake venom. Injury 2015; 46(4):655–660; doi: 10.1016/j. injury.2015.01.031.

34. Tomé RFF, Silva DFB, Dos Santos CAO, et al. ILIB (intravascular laser irradiation of blood) as an adjuvant therapy in the treatment of patients with chronic systemic diseases-an integrative literature review. Lasers Med Sci 2020;35(9):1899–1907; doi: 10.1007/s10103-020-03100-4.

35. Butowt R, Bilin´ska K, von Bartheld C. Why does the omicron variant largely spare olfactory function? Implications for the pathogenesis of anosmia in coronavirus disease 2019. J Infect Dis 2022;226(8):1304–1308; doi: 10.1093/ infdis/jiac113.

36. Legouté F, Bensadoun RJ, Seegers V, et al. Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: Results of a randomised, triple blind, multicentre phase III trial. Radiat Oncol 2019; 14(1):83; doi: 10.1186/s13014-019-1292-2.

37. Gautam AP, Fernandes DJ, Vidyasagar MS, et al. Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. J Photochem Photobiol B 2015; 144:51–56; doi: 10.1016/j.jphotobiol.2015.01.011.

38. de Moraes FB, Pinheiro SL. Photobiomodulation for pain relief after third molar extraction: A randomized doubleblind split-mouth clinical trial. Photobiomodul Photomed Laser Surg 2023;41(7):320–327; doi: 10.1089/photob.2022 .0159.

39. Momeni E, Barati H, Arbabi MR, et al. Low-level laser therapy using laser diode 940nm in the mandibular impacted third molar surgery: Double-blind randomized clinical trial. BMC Oral Health 2021;21(1):77; doi: 10.1186/ s12903-021-01434-1.

40. Whitcroft KL, Hummel T. Olfactory dysfunction in COVID-19: Diagnosis and management. JAMA 2020; 323(24):2512–2514; doi: 10.1001/jama.2020.8391.

41. Fernández-de-Las-Pen˜as C, Palacios-Cen˜a D, Gómez- Mayordomo V, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. Eur J Intern Med 2021;92:55–70; doi: 10.1016/j.ejim.2021.06 .009.

42. Tong JY, Wong A, Zhu D, et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 Patients: A systematic review and meta-analysis. Otolaryngol Head Neck Surg 2020;163(1):3–11; doi: 10.1177/0194599820 926473.

43. Thomas DC, Baddireddy SM, Kohli D. Anosmia: A review in the context of coronavirus disease 2019 and orofacial pain. J Am Dent Assoc 2020;151(9):696–702; doi: 10 .1016/j.adaj.2020.06.039.

44. Borah H, Das S, Goswami A. Otorhinolaryngological manifestations and its management in COVID 19 patients. Indian J Otolaryngol Head Neck Surg 2022;74(Suppl. 2): 3391–3394; doi: 10.1007/s12070-021-02436-9.

45. Chabot AB, Huntwork MP. Turmeric as a possible treatment for COVID-19-induced anosmia and ageusia. Cureus 2021;13(9):e17829; doi: 10.7759/cureus.17829.

46. Chauhan G, Upadhyay A, Khanduja S, et al. Stellate ganglion block for anosmia and dysgeusia due to long COVID. Cureus 2022;14(8):e27779; doi: 10.7759/cureus .27779.

47. Ghods K, Alaee A. Olfactory and taste disorders in patients suffering from Covid-19, a review of literature. J Dent (Shiraz) 2022;23(1):1–6; doi: 10.30476/DENTJODS.2021 .87800.1284.

48. Singh CV, Jain S, Parveen S. The outcome of fluticasone nasal spray on anosmia and triamcinolone oral paste in dysgeusia in COVID-19 patients. Am J Otolaryngol 2021; 42(3):102892; doi: 10.1016/j.amjoto.2020.102892.

49. Singh V, Garg A, Bhagol A, et al. Photobiomodulation alleviates postoperative discomfort after mandibular third molar surgery. J Oral Maxillofac Surg 2019;77(12):2412– 2421; doi: 10.1016/j.joms.2019.06.009.

50. Payne T, Kronenbuerger M, Wong G. Gustatory Testing. StatPearls Publishing. 2023. Available from: https://pub med.ncbi.nlm.nih.gov/33620811/.

51. Rathee M, Jain P. Ageusia. In: StatPearls [Internet]. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/ NBK549775/.

52. Cronshaw M, Parker S, Anagnostaki E, et al. Photobiomodulation and oral mucositis: A systematic review. Dent J (Basel) 2020;8(3):87; doi: 10.3390/dj8030087.

53. Yadav A, Gupta A. Noninvasive red and near-infrared wavelength-induced photobiomodulation: Promoting impaired cutaneous wound healing. Photodermatol Photoimmunol Photomed 2017;33(1):4–13; doi: 10.1111/phpp .12282.