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Efficacy and safety of photobiomodulation combined with oral cryotherapy on oral mucosa pain in patients with burning mouth syndrome: a multi-institutional, randomized, controlled trial

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Abstract

Background The prevalence of burning mouth syndrome (BMS) is approximately 8% in clinical patients; thus, BMS remains a therapeutic challenge. Photobiomodulation (PBM) and oral cryotherapy (OCT) have been evaluated for the treatment of burning pain, but no confirmatory trials have been performed. To evaluate the comparative effectiveness of PBM combined with OCT at reducing pain and psychological distress compared with PBM alone, OCT alone, or drug therapy (DT) alone in a cohort of patients with BMS.

Methods This multi-institutional, single-blinded (assessor-blinded), randomized controlled trial with 4 treatment groups was conducted at Xinhua Hospital, Shanghai Jiao Tong University School of Medicine and Affiliated Stomatology Hospital of Guilin Medical University from December 12, 2022, to January 24, 2024. Among the 156 patients assessed for eligibility, 28 were excluded, and 128 patients with a BMS qualified for randomization to 1 of the 4 treatment groups. The participants received 7 treatment sessions of (1) PBM combined with OCT, (2) PBM, (3) OCT, or (4) DT during a 7-week period. The coprimary outcome measures were changes in visual analogue scale (VAS) scores and the overall response rate between baseline and 7 weeks of treatment.

Results After 7 weeks of treatment, the PBM + OCT group achieved a high overall response rate for pain reduction (81.25%). This difference in pain reduction trends between the groups resulted in a nearly fivefold greater mean change in the VAS score at the 12-week assessment for the PBM + OCT group than for the DT group ($p < 0.0083$). Furthermore, anxiety symptoms were also significantly alleviated by PBM combined with OCT, resulting in a nearly tenfold greater mean change in the GAD-7 score at the 7-week assessment in the PBM + OCT group than in the DT group ($p < 0.0083$). No severe adverse events were reported during the study period.

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Conclusions PBM and OCT combination therapy reduces oral mucosa pain and alleviates anxiety symptoms in patients with BMS; thus, this combination therapy is expected to become a promising pain management option for patients with BMS.

Trial registration Chinese Clinical Trial Registry Identifier: ChiCTR2300074518.

Keywords Burning mouth syndrome, Photobiomodulation, Oral cryotherapy, Pain management, Oral health-related quality of life, Randomized clinical trial

Background

Burning mouth syndrome (BMS) is a complex chronic neuropathic pain disorder that is characterized by generalized or localized intraoral pain or a burning sensation in an otherwise healthy-appearing oral mucosa without any evidence of specific mucosal lesions and/or laboratory findings [1]. The absence of objective clinical and pathological manifestations associated with pain symptoms makes it challenging for BMS patients to comprehend these symptoms, thus potentially leading to delays in diagnosis and even worsening of symptoms [2]. The global prevalence of BMS is 1.73% in the general population and almost 8% in clinical patients, and this disorder mainly affects women who are middle-aged and older and women who are peri- and postmenopausal [3]. Previous studies have suggested that chronic pain may have a detrimental effect on patients' physical and mental health via disruptions in the neuroendocrine system and abnormalities in the brain's endogenous pain modulation and mood-regulating systems [4, 5]. Chronic pain in BMS patients is often associated with psychological distress, such as anxiety, depression [6], and poor sleep quality [7], all of which can result in poor oral health-related quality of life (OHRQoL) [8]. Therefore, the chronicization of pain due to BMS often poses a major therapeutic challenge.

A position paper from the Chinese Society of Oral Medicine revealed that low-quality evidence supported the effect of drug therapy (DT) in patients with BMS, including gargling with 2–4% sodium bicarbonate solution, oral administration of mecobalamin tablets, topical or oral administration of clonazepam, etc. [9]. Mecobalamin can enhance neuronal methylation and accelerate nerve cell growth, leading to neuroprotective effects [10]. Studies have demonstrated that oral mecobalamin tablets can promote peripheral nerve regeneration and improve clinical symptoms such as neuropathic pain [10, 11]. A previous network meta-analysis [12] that included 44 trials suggested that oral administration of clonazepam probably reduces the pain associated with BMS compared with placebo. The effects of topical or oral clonazepam are believed to be exerted through its agonistic action on gamma amino butyric acid (GABA) A receptors; a study has suggested that topical application of GABA analogues reduces similar experimental burning pain [13]. While previous studies have supported the effectiveness of DT for providing pain relief in patients with BMS, the studies were limited in quantity and had small sample sizes [14]. In addition, owing to the impact of the chronicization of pain on emotional regulation among BMS patients, psychological interventions for improving pain perception have also been found to be effective in ameliorating psychological symptoms such as anxiety and depression in patients (based on very low-quality evidence) [15, 16]. Although the abovementioned DTs and psychological interventions have been preliminarily applied for treating BMS and have achieved considerable outcomes, these treatments have yet to be fully elucidated [17, 18].

Noninvasive physical therapy modalities are important innovations in pain management and have been used to treat a series of oral mucosal diseases, including recurrent aphthous stomatitis [19], oral mucositis [20], and oral lichen planus [21]. Photobiomodulation (PBM) is a noninvasive and safe physical therapy modality that has the advantages of fewer side effects and good tolerance [22]. PBM has positive effects on the control of neuropathic pain, such as diabetic peripheral neuropathy [23] and trigeminal neuralgia [24, 25]. Furthermore, the use of PBM to treat BMS has been examined in a preliminary study [26, 27]. Previous meta-analyses have yielded very low- to low-quality evidence and revealed that PBM may also represent an effective therapy for alleviating oral mucosal pain or burning sensations in patients with BMS compared with placebo [28, 29]. However, even though PBM has improved oral mucosal pain in BMS patients, its clinical significance may be limited, possibly due to the lower intensity or frequency of interventions. Therefore, a randomized controlled trial based on this evidence is necessary. Another evidence-supported physical therapy modality, i.e. cooling the mucosa with oral cryotherapy (OCT), which is a non-invasive, safe, inexpensive, and easily applied intervention approach, has also been shown to alleviate oral mucosal pain or burning sensations [30, 31]. Although OCT has been widely used in investigations on oral pain reduction and mucositis prevention in cancer patients receiving chemotherapy [31],

there is a lack of clinical trials examining the use of OCT for the management of BMS.

Although PBM and OCT are safe and effective and abundant scientific evidence has demonstrated that both therapies significantly reduce pain or burning sensations, the majority of patients with BMS receive very limited access to physical therapy facilities. Therefore, these services must be arranged more effectively. Moreover, PBM and OCT have been widely used in patients with oral mucosal diseases, and numerous studies have confirmed that these therapies are safe and feasible and have high patient compliance. However, it remains unclear whether PBM and OCT combination therapy is superior to PBM alone, OCT alone, or DT. Therefore, the aim of this clinical trial was to investigate the efficacy and safety of PBM combined with OCT for pain reduction in the oral mucosa of patients with BMS undergoing a 7-week intervention and a 5-week follow-up. Additionally, this study aimed to assess the potential benefits of PBM combined with OCT on anxiety, depression, sleep quality, and OHRQoL.

Methods

Study design and participants

This multi-institutional, single-blinded (assessor-blinded), randomized controlled trial was conducted across 2 clinical sites in China based on competitive enrolment from December 12, 2022, to January 24, 2024. The study was performed in accordance with the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines (https://www.spirit-statement.org) [32] and the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org) [33]. The study protocol and informed consent form were reviewed and approved by the ethics committees of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (XHEC-C-2022-085-3) and the Affiliated Stomatology Hospital of Guilin Medical University (KQ-0035). Furthermore, the study was conducted in accordance with the Declaration of Helsinki. The study was registered with the Chinese Clinical Trial Register Network (registration number: ChiCTR2300074518). Written informed consent for publication was obtained from all participants.

Patients were diagnosed with BMS according to the International Classification of Headache Disorders-3 (ICHD-3) (2018) [34]. The inclusion criteria were as follows: (1) aged > or = 18 years; (2) experienced burning pain of the oral mucosa for more than 2 h a day for more than 3 months as their chief complaint; (3) showed no obvious abnormalities on the oral mucosal surface during clinical examination; and (4) had no local or systemic causes found for burning pain in the oral mucosa, such as oral mucositis, oral candidiasis, geographic tongue, Sjögren's syndrome, diabetes mellitus, anaemia, or cerebrovascular disease. The exclusion criteria were as follows: (1) had organic lesions causing pain in the oral mucosa, dental tissues or periodontal tissues that could be detected, such as recurrent aphthous stomatitis, deep caries, acute pulpitis, and periodontitis; (2) had a history of orofacial neuralgia, such as trigeminal neuralgia and glossopharyngeal neuralgia; (3) had a history of head and neck radiotherapy, accompanied by salivary gland diseases or other oral mucosal diseases; (4) had severe diseases of important organs such as the heart, liver, kidney and blood system; (5) were pregnant or lactating; and (6) had contraindications to physical therapy, such as acute inflammation, hyperthermia, bleeding tendency, or malignancy.

Random assignment and blinding

All participants who met the inclusion criteria were randomized and assigned to one of four treatment groups—the PBM + OCT group, the PBM group, the OCT group, or the DT group—at a ratio of 1:1:1:1. The names of the treatment groups were placed into envelopes according to the randomization sequence, sealed, and labelled with a sequential participant number. Once a patient provided consent to participate and signed the informed consent form, a researcher opened the envelope to reveal the name of the assigned group. The group assignment was then be confirmed by another researcher. Finally, these outcomes were approved and analysed by another assessor who was involved in this process and had no role in the study design, group allocation, or data collection.

Procedures

Figure 1 shows the treatment protocol for eligible patients. Each patient underwent one outpatient visit per week for a total of 7 weeks (i.e. week 1 to week 7). Week 1 served as the baseline period, and the first treatment began immediately at week 1. Follow-up assessments were scheduled for week 8 and week 12. In week 1, a 10-min education session was provided to all participants on the aetiology, symptoms, and treatment information regarding BMS.

For patients with BMS, the treatment protocols were as follows: (1) PBM + OCT group: PBM: The entire procedure was performed by professional physical therapists. A photobiomodulation (PBM) device (HJZ-3A, continuous mode, Chengdu, China) was used, with a wavelength of 632.6 nm and a power output of 25 mW. From the 32 potential application points shown in Fig. 2, we selected 10 points per patient based on the symptomatic areas identified during the clinical evaluation. Each selected point was exposed

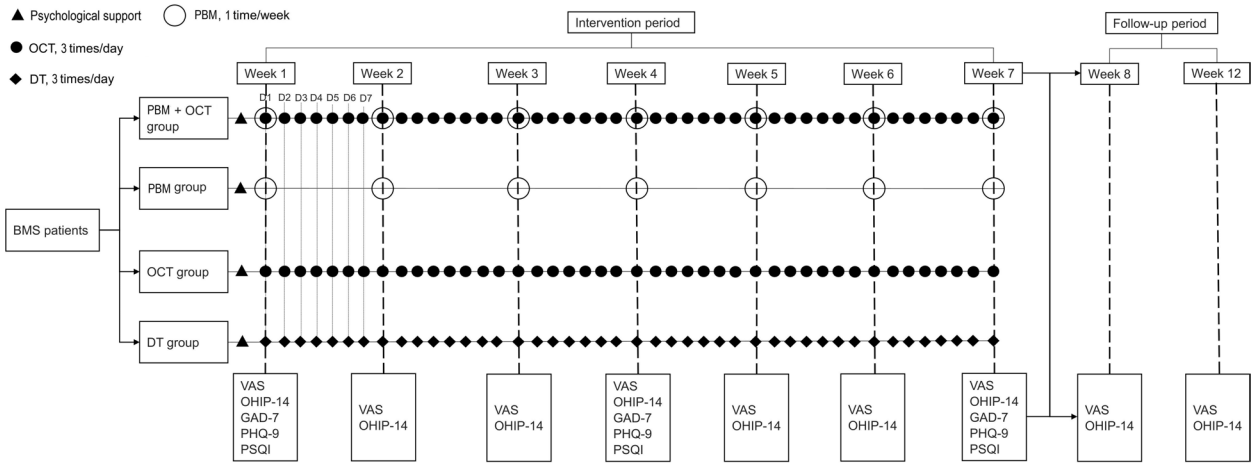

Fig. 1 Treatment protocol for eligible patients. Patients randomly assigned to the PBM + OCT group received PBM and OCT, those in the PBM group received PBM alone, those in the OCT group received OCT alone, and those in the DT group received DT alone. PBM was administered once a week for 7 weeks as a cycle. OCT or DT was administered 3 times a day (after breakfast, after lunch, and after dinner). Week 1 represents the baseline assessment. In week 1, a 10-min education session was provided to all participants. Abbreviations: *BMS* burning mouth syndrome, *D* day, *DT* drug therapy, *GAD-7* Generalized Anxiety Disorder 7-item scale, *OCT* oral cryotherapy, *OHIP-14* Oral Health Impact Profile-14, *PBM* photobiomodulation, *PHQ-9* Patient Health Questionnaire-9, *PSQI* Pittsburgh Sleep Quality Index Scale, *VAS* Visual Analogue Scale

to irradiation for 1 min, resulting in a total treatment duration of 10 min. The probe was positioned approximately 10 mm from the oral mucosa, covering an area of approximately 0.5 cm^2. Consequently, the irradiance = 25 mW/0.5 cm^2 = 50 mW/cm^2. The total dose = 0.025 W × 600 s = 15 J. Divided equally between the 10 areas, each area received 15/10 = 1.5 J with a corresponding fluence of 3 J/cm^2 [35]. Each patient underwent one PBM irradiation session per week for 7 weeks. A regular schedule was established for the calibration and maintenance of the laser to ensure its accuracy and performance. OCT: The OCT procedure was conducted at home; therefore, it was initiated following the PBM procedure. Each patient underwent oral cryotherapy three times a day (after breakfast, after lunch, and after dinner) for a minimum of 5 min per session, with at least 5 days of sessions per week for 7 weeks. Patients were guided to use standardized ice moulds to create ice balls with a diameter of approximately 20 mm, which is a suitable size for intraoral movement. When performing OCT, it is important to place an ice ball in the area of oral mucosal pain and maintain continuous cooling of the intraoral temperature. (2) In the PBM group, the specific PBM protocol was the same as that in the PBM + OCT group. (3) In the OCT group, the specific OCT protocol was the same as that in the PBM + OCT group. (4) In the DT group, patients were orally administered 0.5 mg of mecobalamin tablets three times a day, followed by gargling with a 2% sodium bicarbonate solution (approximately 10 ml per dose) three times a day for 7 weeks according to the guidelines outlined in the Management of Burning Mouth Syndrome position paper by the Chinese Society of Oral Medicine [9].

Study outcomes and endpoints

The coprimary outcome measures were the change in visual analogue scale (VAS) scores and the overall response rate between baseline and 7 weeks of treatment [36, 37]. The change in VAS score was calculated by subtracting each of the posttreatment assessment values from the baseline values. The overall response rate was calculated via the following formula: overall response rate $(\%) = (VAS_{baseline} - VAS_{week\ 7})/VAS_{baseline} \times 100\%$ [27]. As the minimum clinically important difference (MCID) for pain reduction was suggested to be set as a change greater than 23% [38], the overall response rate was divided into two grades according to the percentage: < 23% was ineffective, or ≥ 23% was effective. Pain levels are categorized as follows: mild pain (< 4 points), moderate pain (4–7 points), and severe pain (> 7 points).

The secondary outcomes included OHRQoL and psychological distress related to BMS. OHRQoL was measured via the Oral Health Impact Profile-14 (OHIP-14) [39]. Psychological distress, including anxiety, depression, and sleep quality, was evaluated by the Generalized Anxiety Disorder 7-item scale (GAD-7) [40], the Patient Health Questionnaire-9 (PHQ-9) [41], and the Pittsburgh Sleep Quality Index (PSQI) [42], respectively. The safety of the treatment was assessed by the incidence of adverse events (AEs) throughout the study.

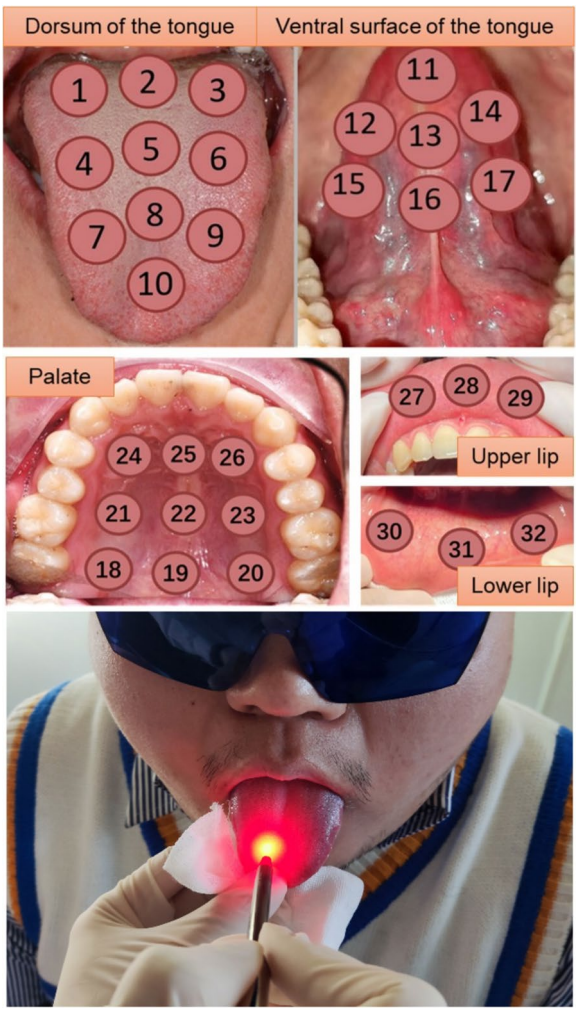

Fig. 2 Illustration of the irradiation points of the oral mucosa. The mucosa of the tongue is mainly divided into 17 irradiation points (numbered 1–17), the mucosa of the palate is roughly divided into 9 irradiation points (numbered 18–26), and the mucosa of the upper and lower lips is roughly divided into 6 irradiation points (numbered 27–32)

Sample size estimation

Power Analysis and Sample Size (PASS 15) software (NCSS LCC., Kaysville, UT, USA) was used for sample size estimation. In accordance with the previous studies [9, 27], we set the overall response rates as 90%, 85%, 60%, and 45% for the PBM + OCT group, PBM group, OCT group, and DT group, respectively. The estimated sample size in each group was 25 (contingency table, chi-square tests), with a power of 80. The two-sided type-I error was 0.0083 [43]. Considering a potential 20% dropout rate, a total sample size of 128 was considered appropriate.

Statistical analysis

Categorical data are reported as numbers with percentages and were analysed via the chi-square test. Normally distributed continuous variables are described as the mean ± standard deviation (mean ± SD). Repeated-measures analysis of variance (ANOVA) was used for comparisons between groups, and a paired-sample *t* test was employed to analyse the difference in outcomes before and after the intervention in each group. Data were also compared between the baseline assessment and each posttreatment follow-up assessment within each group via repeated-measures ANOVA. Skewed distributed data are described as medians with interquartile ranges (IQRs), and the Wilcoxon rank-sum test was used for comparisons between groups and before and after intervention in each group. In addition, the difference between the outcome measures of each group before and after the intervention was calculated, and an independent-sample *t* test was used to analyse the difference between the groups if the data were normally distributed; otherwise, the Wilcoxon rank-sum test (Kruskal–Wallis H test) was used to compare nonnormally distributed data. We used intention-to-treat (ITT) analysis according to group allocation as the main analytical method in this study and included all patients who were randomly assigned, regardless of whether they received treatment. Statistical analysis was performed via the software package 26.0 (SPSS, Chicago, USA). p values < 0.0083 were considered to indicate statistical significance, and the Bonferroni method was used for multiple comparisons.

Results

Patient characteristics

A total of 156 adult patients with BMS were screened for enrolment between December 12, 2022, and January 24, 2024. Among these patients, 21 patients did not meet the inclusion criteria, and 7 patients declined to participate in the trial. The remaining 128 participants were included in the ITT population and randomized to receive one of 4 treatments: PBM + OCT ($n = 32$), PBM ($n = 32$), OCT ($n = 32$) or DT ($n = 32$). After randomization, 5 patients withdrew consent of their own volition, and they did not receive the full treatment course or complete follow-up examinations. Therefore, these 5 patients were excluded from the safety analysis. The ITT analysis included 128 originally recruited patients with BMS. Figure 3 shows the flow diagram of this study.

The ITT population comprised 10 male and 118 female patients with a mean age of 59.94 ± 11.99 years and a median disease duration of 6 months (IQR, 3–17.5). There were no significant differences in the baseline characteristics among the 4 groups ($p > 0.0083$). Most of the

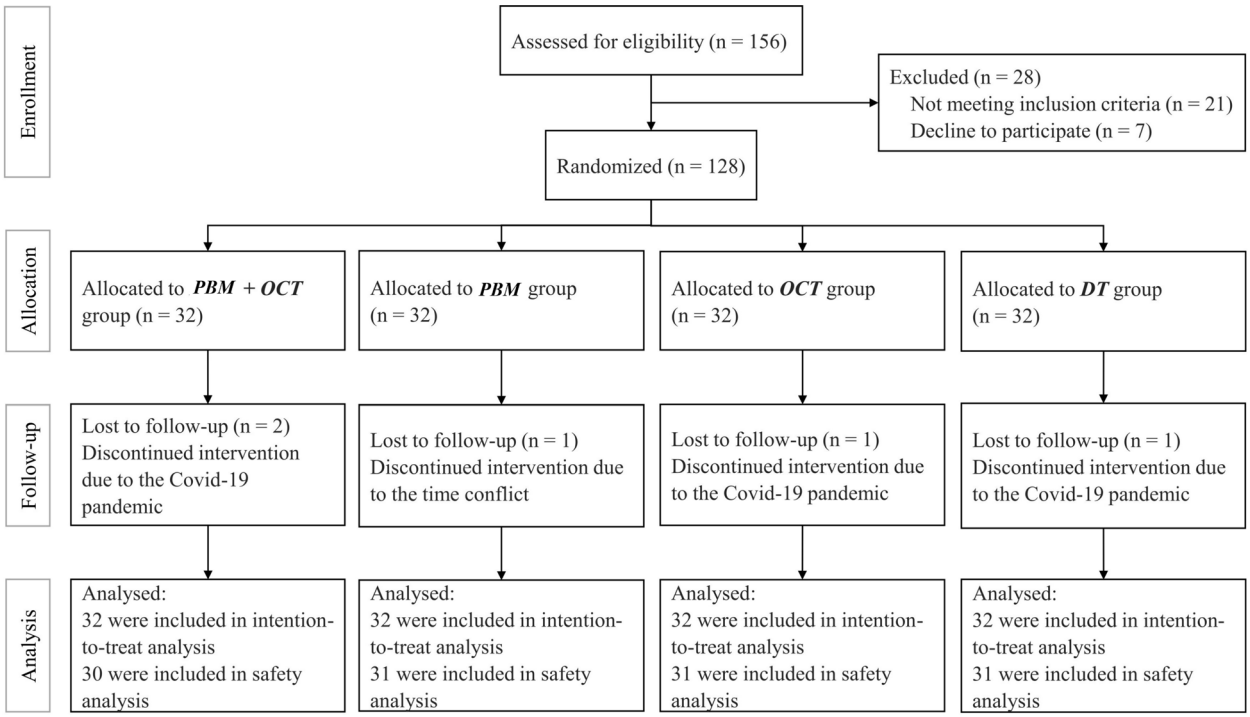

Fig. 3 Flowchart of patients. Prerecruitment assessments were performed in 156 patients with BMS, resulting in 28 patients being excluded before recruitment and 128 patients being included in the study. At the end of the study, 30 patients in the PBM + OCT group, 31 patients in the PBM group, 31 patients in the OCT group, and 31 patients in the DT group completed the 12-week follow-up. Intention-to-treat (ITT) analysis was performed, including the 128 originally recruited patients with BMS. No severe adverse events were reported during this study. Abbreviations: *DT* drug therapy, *OCT* oral cryotherapy, *PBM* photobiomodulation

patients (95.31%) had mild to moderate pain in the oral mucosa, with a mean VAS score of 4.06 ± 2.14 points. Among the 128 patients with BMS, the mean OHIP-14 score was 9.46 ± 7.39 points, the mean GAD-7 score was 7.49 ± 6.14 points, the mean PHQ-9 score was 4.68 ± 4.46 points, and the mean PSQI score was 7.49 ± 4.19 points (all $p > 0.0083$) (Table 1). The oral symptoms and psychological distress of patients with BMS can be found in Additional file 1: Table S1 and Table S2.

Primary outcomes

Change in VAS scores over time

In the PBM + OCT group, PBM group, and OCT group, the reduction in VAS score increased during the study. This difference in pain reduction trends between the groups resulted in a nearly fivefold greater mean change in the VAS score at the 12-week assessment for the PBM + OCT group than for the DT group ($p < 0.0083$) (Fig. 4).

The overall response rate for pain

The overall response rates for pain among the 4 groups at week 7 were 81.25% in the PBM + OCT group, 68.75% in the PBM group, 78.13% in the OCT group, and 56.25% in the DT group. The difference in response rates between the groups was not statistically significant ($\chi^2 = 4.961$, $p > 0.0083$) (Table 2).

Secondary outcomes

Change in the GAD-7, OHIP-14, PHQ-9, and PSQI scores

Next, the changes in the GAD-7, OHIP-14, PHQ-9, and PSQI scores at 7 or 12 weeks within and between the groups were examined. In the PBM + OCT, PBM, and OCT groups, the differences from baseline tended to increase over the course of the study for the GAD-7, OHIP-14, PHQ-9, and PSQI scores. In contrast, the DT group demonstrated relatively less improvement in the GAD-7, OHIP-14, and PHQ-9 scores. Anxiety symptoms were also significantly alleviated by PBM combined with OCT, resulting in a nearly tenfold greater mean change in the GAD-7 score at the 7-week assessment in the PBM + OCT group than in the DT group ($p < 0.0083$) (Fig. 5).

Adverse events

The safety analysis included 123 patients who received a full treatment course or completed the follow-up examinations. Five patients reported adverse events during the

Table 1 General characteristics of patients with BMS at baseline

Characteristic	PBM + OCT group (*n* = 32)	PBM group (*n* = 32)	OCT group (*n* = 32)	DT group (*n* = 32)	All (*n* = 128)	*p* value
Age, mean ± SD, years	63.28 ± 10.15	57.59 ± 13.02	58.88 ± 12.60	60.00 ± 11.79	59.94 ± 11.99	0.267
Gender, female, *n* (%)	30 (93.75)	27 (84.38)	26 (81.25)	27 (84.38)	110 (85.94)	0.524
Menopausal women [a], *n* (%)	23 (76.67)	17 (62.96)	18 (69.23)	19 (70.37)	77 (70.00)	0.734
Menopause period [b], mean ± SD, years	14.35 ± 6.42	11.71 ± 8.23	12.33 ± 9.61	15.74 ± 8.49	13.64 ± 8.15	0.422
BMI, kg/m^2, mean ± SD	22.20 ± 2.26	22.44 ± 3.01	22.04 ± 2.45	22.98 ± 3.19	22.41 ± 2.75	0.542
Occupation, retirement, *n* (%)	25 (78.13)	16 (50.00)	19 (59.38)	18 (56.25)	78 (60.94)	0.116
Level of education, *n* (%)						
Junior high and below	17 (53.13)	19 (59.38)	16 (50.00)	20 (62.50)	72 (56.25)	0.477
High school or junior college	13 (40.63)	8 (25.00)	9 (28.13)	9 (28.13)	39 (30.49)	
College and above	2 (6.25)	5 (15.63)	7 (21.88)	3 (9.38)	17 (13.28)	
Disease duration [c], median (IQR), months	8.5 (4.25–21.25)	5.5 (3.00–14.25)	6 (3.00–16.5)	8 (3.25–22.5)	6 (3.00–17.5)	0.420
VAS score, mean ± SD	4.02 ± 2.27	4.13 ± 2.24	3.91 ± 2.02	4.20 ± 2.10	4.06 ± 2.14	0.951
OHIP-14 score, mean ± SD	10.53 ± 7.03	7.97 ± 6.59	9.41 ± 6.48	9.94 ± 9.23	9.46 ± 7.39	0.555
GAD-7 score, mean ± SD	7.44 ± 6.03	6.94 ± 6.27	9.25 ± 6.79	6.34 ± 5.29	7.49 ± 6.14	0.263
PHQ-9 score, mean ± SD	5.00 ± 4.36	3.69 ± 4.72	5.06 ± 3.40	4.97 ± 5.23	4.68 ± 4.46	0.553
PSQI score, mean ± SD	8.47 ± 3.48	6.75 ± 4.91	7.78 ± 4.02	6.97 ± 4.17	7.49 ± 4.19	0.337

Abbreviations: *BMS* burning mouth syndrome, *DT* drug therapy, *GAD-7* Generalized Anxiety Disorder 7-item scale, *OCT* oral cryotherapy, *OHIP-14* Oral Health Impact Profile-14, *PBM photobiomodulation*, *PHQ-9* Patient Health Questionnaire-9, *PSQI* Pittsburgh Sleep Quality Index Scale, *VAS* Visual Analogue Scale

IQR, the interquartile range; mean ± SD, mean ± standard deviation

[a] Menopausal women: the proportion of menopausal women among all female patients

[b] Menopause period: the period from the onset of menopause to the present day

[c] Disease duration: the period from the onset of initial BMS-related symptoms to the time of diagnosis

study period, resulting in an overall adverse event rate of 4.07%. No severe adverse events were reported during the study period. Adverse events during treatment in each group are shown in Additional file 2: Table S3.

Discussion

This study is the first multi-institutional, randomized controlled trial to investigate the efficacy and safety of PBM combined with OCT for the treatment of oral mucosa pain in patients with BMS. Our results demonstrated that PBM combined with OCT may yield a greater overall response rate in terms of pain reduction than PBM alone, OCT alone, or DT. After 7 weeks of combination therapy, patients with BMS experienced an effective reduction in oral mucosa pain, and this positive effect reached an MCID with beneficial effects and may be sustained over a longer period.

Pain is a very complex individual experience involving physiological, sensory, affective, cognitive, behavioural, and sociocultural factors [44]. Pain, psychological issues, and sleep disorders overlap and are intertwined in BMS, resulting in complex psychological distress and poor quality of life [45]. BMS-related pain is considered a form of neuropathic pain and can result from disorders of the peripheral or central nervous system [46]. Puhakka et al. [47, 48] observed the density of nerve fibres in the epithelial layer of the tongue mucosa in patients with BMS and healthy controls via microscopy. They reported a significant reduction in the density of intraepithelial nerve fibres in BMS patients compared with healthy controls, along with diffuse morphological changes in the nerve fibres indicative of axonal degeneration [49]. Additionally, there was a significant increase in the density of TRPV-1-positive nerve fibres and nerve growth factor (NGF) fibres, suggesting possible sensory nerve dysfunction in the tongue [50]. However, some studies have shown that the density and integrity of peripheral nerve fibres in the tongue of BMS patients may remain unchanged, which may suggest the possibility of centrally mediated pain [51]. Additionally, subclinical inflammation leading to disrupted cytokine levels, such as the upregulation of proinflammatory cytokines such as IL-6 and IL-8, was observed in the saliva or plasma of BMS patients [52, 53]. Since this type of pain is influenced by multiple factors, patients may not respond significantly to unidimensional interventions or may experience only limited relief. One study suggested that a multidisciplinary approach can be utilized to manage neuropathic pain, and some therapies for treating neuropathic pain have been investigated and compared with positive outcomes [54].

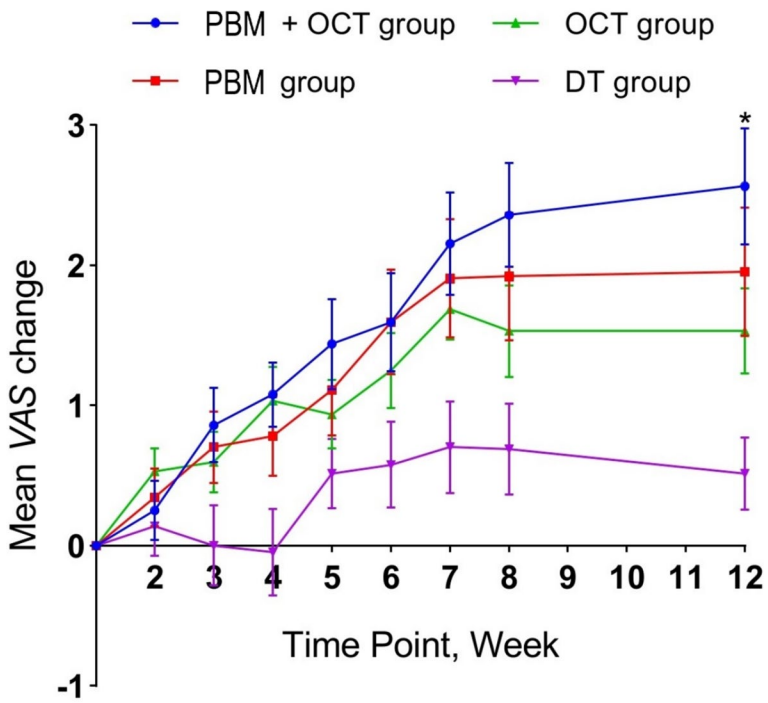

Fig. 4 The mean change in the VAS score at different time points. The *X*-axis shows the time points (weeks) of the intervention and follow-up, with "1" representing the baseline assessment. The *Y*-axis shows the mean change in the values of the scores, as calculated by subtracting the baseline values from each of the posttreatment assessment values. * indicates that the improvement in VAS scores for the PBM + OCT group was significantly greater than that observed in the DT group at the 12-week assessment ($p < 0.0083$). Abbreviations: *DT* drug therapy, *OCT* oral cryotherapy, *PBM* photobiomodulation, *VAS* Visual Analogue Scale

Table 2 The overall response rate to pain reduction before and after the 7-week intervention in the BMS patients in each group

Outcomes, n (%)	PBM + OCT group ($n = 32$)	PBM group ($n = 32$)	OCT group ($n = 32$)	DT group ($n = 32$)	All ($n = 128$)
Overall response rate	26 (81.25)	22 (68.75)	25 (78.13)	18 (56.25)	91 (71.09)
χ^2 value	5.892				
p value	0.117				

Abbreviations: *BMS* burning mouth syndrome, *DT* drug therapy, *OCT* oral cryotherapy, *PBM* photobiomodulation

A response was characterized by a reduction in the VAS score > or = 23%

PBM triggers a photochemical reaction in the cell via infrared or near-infrared light and produces photobiomodulatory and neuroprotective effects [55, 56]. OCT can produce a cooling effect, which lowers the mucosal temperature and affects oral haemodynamics [57], and may decrease nerve conduction velocity and increase the pain threshold and pain tolerance to reduce the burning sensation [58]. A previous study revealed that PBM can reduce pain and burning sensations by regulating thermoregulation, neurogenic inflammation, and thermal sensitivity in animal models of neuropathic pain [59]. The current perspective within the photobiomodulation community emphasizes the involvement of multiple pathways of operation, including wavelength, irradiance, and dosimetry. It has been reported that longer wavelengths within the range of 780–950 nm, which penetrate deeper tissues, are utilized for treating tissues located at greater depths, whereas wavelengths in the range of 600–700 nm are used for treating more superficial tissues [60]. Dosimetry plays a crucial role in pain management, with infrared wavelengths and higher dosages potentially activating TRPV1 membrane ion channels [61] and cytochrome c oxidase [62], which is considered important in pain prevention. PBM appears to require dosimetry between 0.05 and 10 J/cm^2; dosimetry greater than 10 J/cm^2 is related to a bioinhibitory effect, as reported by the Guide for

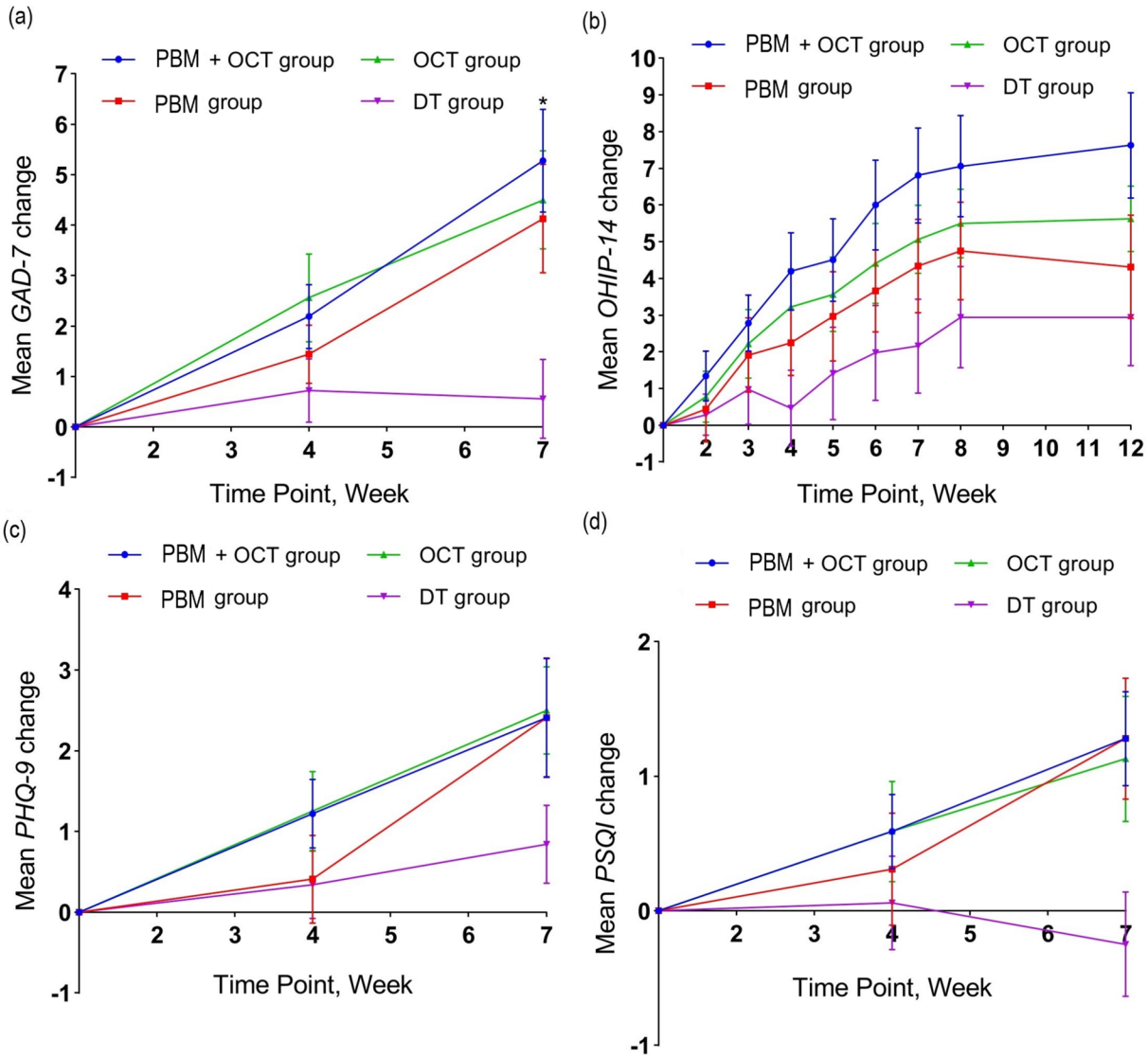

Fig. 5 The mean changes in GAD-7 (**a**), OHIP-14 **(b)**, PHQ-9 (**c**), and PSQI (**d**) scores at different time points. The *X*-axis shows the time points (weeks) of the intervention and follow-up, with "1" representing the baseline assessment. The *Y*-axis shows the mean change in the values of the scores, as calculated by subtracting the baseline values from each of the posttreatment assessment values. **a** Asterisk indicates that the improvement in GAD-7 scores in the PBM + OCT group was significantly greater than that observed in the DT group at the 7-week assessment ($p < 0.0083$). Abbreviations: *DT* drug therapy, *GAD-7* Generalized Anxiety Disorder 7-item scale, *OCT* oral cryotherapy, *OHIP-14* Oral Health Impact Profile-14, *PBM* photobiomodulation, *PHQ-9* Patient Health Questionnaire-9, *PSQI* Pittsburgh Sleep Quality Index Scale

Photobiomodulation Therapy in Oral Medicine [35]. The parameters that determine more evident clinical effects are in the range of dosimetry of 1–10 J/cm^2, but values between 1 and 5 J/cm^2 are also acceptable. Arbabi-Kalati et al. (1 J/cm^2) [63] and Pezelj-Ribaric et al. (3 J/cm^2) [64] also achieved favourable clinical outcomes with lower doses of PBM, and our study further supported these previous findings. Irradiance, another critical factor, can facilitate stimulation and healing at relatively low doses (5 to 50 mW/cm^2), while higher doses (up to 50 mW/cm^2) may be advantageous for nerve inhibition and pain relief [65]. Furthermore, the use of PBM, which may also downregulate the levels of IL-6 and IL-8, may achieve beneficial biomodulatory effects [63, 66, 67].

Our findings are generally consistent with those of Sun et al., who reported that all 21 BMS patients in the PBM group demonstrated a significant decrease in VAS score (ranging from 2 to 100%, with a mean reduction of 52%) [27]. A recent study by Finfter et al. reported a significant decrease in the VAS score (from 7.80 ± 1.83 to 2.07 ± 2.55)

in 30 BMS patients after 10 weeks of PBM [68]. Our study expanded on this evidence base by including a larger sample size with more groups and assessments at 9 different time points, including 7 treatment assessments and 2 follow-up assessments over 12 weeks in a randomized controlled trial. Previous meta-analyses reported that more or longer PBM interventions were positively associated with pain relief in BMS patients and could achieve the MCID of a beneficial effect [12]. Notably, the findings of this study indicate that there was no significant difference in pain reduction between OCT alone and PBM alone. The combined application of PBM and OCT may be more effective, with an earlier onset of effect and longer efficacy; this implies that combination therapy may offer superior results compared with either treatment alone. One possible explanation for the synergistic effect of PBM combined with OCT for the treatment of BMS is that PBM exerts a neuroprotective effect [69], whereas OCT could provide an additional effect by lowering the oral temperature, thereby alleviating the burning sensation [70].

Furthermore, our study suggested that PBM and OCT combination therapy may offer even greater benefits for anxiety symptoms. PBM is not only available for the management of chronic pain [71] but also recommended for anxiety disorders [72]. A prior meta-analysis revealed that PBM had a positive effect on negative emotions in patients with BMS compared with placebo, but these effects were not statistically or clinically significant [29]. This trial expanded on this evidence base and indicated that PBM combined with OCT may be more effective than other interventions. The intertwining and mutual influence of pain with anxiety symptoms may explain why the application of anxiolytics (such as clonazepam or melatonin) [73] or psychological interventions [74] can also improve both the anxiety symptoms and pain of some BMS patients. Some BMS patients who received PBM combined with OCT similarly improved anxiety symptoms and pain in this study, indicating that the improvement in anxiety symptoms may have been associated with a reduction in clinical pain levels.

These results suggest that the combination of PBM with OCT has a positive effect on OHRQoL. The characteristics of OHRQoL in patients with BMS indicate that its improvement and rehabilitation involve many various aspects and may require more prolonged and more multidisciplinary interventions [29, 75]. Spanemberg et al. [26] reported that the efficacy of patients who received PBM 3 times per week significantly differed from that of those who received placebo, possibly indicating that a more intense frequency of intervention, that is, multiple interventions per week, may be more conducive to improving OHRQoL.

In terms of depressive symptoms, a study suggested that more stress factors and higher stress biomarker levels of cortisol, α-amylase, IgA and IL-8 biomarkers [53], especially the plasma IL-8 signature [76] and salivary cortisol levels [77], significantly correlated with depressive symptomatology in patients with BMS than in controls. Although previous studies have shown that the expression of IL-8 and cortisol is reduced after the application of PBM and contributes to an improvement in burn symptoms [66, 78], PBM does not appear to have a clinically significant beneficial effect on depressive symptoms related to BMS. Moreover, although PBM has been constituted as an innovative treatment for major depressive disorder, there is only weak support for its promising role in the treatment of depressive symptoms [79]. Given the lack of studies on the improvement of depressive symptoms related to BMS, more targeted comprehensive psychological interventions are needed in the future.

Almoznino et al. [80] reported that 50% to 70% of chronic pain patients reported sleep disturbances, with the majority attributing their sleep problems solely to pain. Although the direct causal relationship between BMS and sleep disturbances cannot be determined, increasing evidence supports the association between sleep disturbances and BMS symptoms [81, 82]. This trial revealed that PBM combined with OCT does not achieve an MCID with beneficial effects on sleep quality; this could be attributed to the fact that sleep conditions can be influenced by many factors, including systemic diseases, mental health issues, environmental influences and psychosocial factors [83]. Previous studies have suggested that it may be beneficial to consider adopting a chronic pain sleep management model for BMS patients, such as cognitive behavioural therapy for insomnia, which has been shown to be an effective treatment for improving sleep in chronic pain patients [84]. Thus, preliminary research can explore its efficacy in the comprehensive management of BMS.

This study has several limitations. First, this study has a relatively short follow-up time, consisting of only 5 weeks, indicating that further insights into long-term and sustained effects are needed. Second, subjective pain reports from patients may be easily influenced by underlying emotional factors and may vary between individuals. Third, this trial did not include a placebo PBM group, as patients can easily observe whether they are undergoing PBM. Future studies need to conduct longer follow-up studies and establish a placebo control group to clarify the short-term and long-term efficacy of PBM.

Conclusions

This trial provided evidence that PBM and OCT combination therapy significantly reduced oral mucosa pain and anxiety symptoms in patients with BMS within 7 weeks of intervention and may contribute to enhancing OHRQoL. These findings therefore contribute to the evidence regarding the benefits of PBM combined with OCT for the improvement of BMS-related pain, providing a preliminary evidence-based foundation for the clinical management of BMS, which is expected to become a promising pain management option. While the combination of PBM and OCT has demonstrated promising outcomes in alleviating symptoms of BMS, additional large-scale clinical trials are imperative to establish conclusive evidence-based protocols. Subsequent studies could explore the potential efficacy of PBM combined with OCT in managing pain among patients with BMS in greater depth.

Abbreviations

AEs	Adverse events
ANOVA	Analysis of variance
BMS	Burning mouth syndrome
CONSORT	Consolidated Standards of Reporting Trials
DT	Drug therapy
GABA	Gamma amino butyric acid
GAD-7	Generalized Anxiety Disorder 7-item scale
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICHD-3	International Classification of Headache Disorders-3
IQRs	Interquartile ranges.
ITT	Intention-to-treat
MCID	Minimum clinically important difference
OCT	Oral cryotherapy
OHIP-14	Oral Health Impact Profile-14
PBM	Photobiomodulation
PHQ-9	Patient Health Questionnaire-9
PSQI	Pittsburgh Sleep Quality Index
SPIRIT	Standard Protocol Items: Recommendations for Intervention Trials
VAS	Visual Analogue Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04015-z.

Supplementary Material 1: Table S1 and Table S2 Oral symptoms in patients with BMS; the OHRQoL and psychological distress in patients with BMS.

Supplementary Material 2: Table S3 Adverse events during treatment in each group.

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Authors' contribution

CHL, XZ, and CLY contributed equally to the manuscript and share first authorship. QD and GYT contributed equally to the manuscript and share correspondent authorship. GYT and QD contributed to the conception and design of the work. CHL, XZ, CLY, XXJ, ZFH, QD, and GYT contributed to the acquisition of the data. CHL, XZ, CLY, XL, QD, and GYT contributed to the analysis and interpretation of the data. CHL, XZ, CLY, XL, QD, and GYT drafted the manuscript. All authors were involved in patient and data management, conceived and (locally) supervised the study, interpreted the data, and revised the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (XHEC-C-2022-085-3) and the Affiliated Stomatology Hospital of Guilin Medical University (KQ-0035).

Consent for publication

The images in Fig. 2 have been anonymized and that written informed consent for publication was obtained from the participants.

Competing interests

The authors declare no competing interests.

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