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Photobiomodulation for the prevention of oral side effects secondary to head and neck cancer therapy: results of a randomised, single-blind clinical trial

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ABSTRACT

Introduction: A significant increase of 61.6 % in new cases of head and neck cancer (HNC) worldwide is projected by 2050. Multimodal treatments for HNC often result in debilitating oral side effects like oral mucositis (OM). Photobiomodulation (PBM) therapy shows promise in managing these side effects, yet standardized protocols are lacking. This randomized clinical trial aims to evaluate PBM's effectiveness in preventing and treating oral side effects and related symptoms in HNC patients.

Methods: We compared PBM with standard treatment in HNC patients at a single centre. PBM efficacy was evaluated on OM, pain, dysgeusia, hyposalivation, dry mouth, and trismus. Additionally, we controlled for analgesic use and fungal infection presence. The study adhered to the CONSORT checklist, is registered on the ClinicalTrials platform, and statistical analysis was performed using SPSS.

Results: The study included 53 patients. The PBM group experienced a significant reduction in OM progression, better salivary function preservation, and lower severity of pain and dysgeusia by the end of treatment. However, no significant differences were found between the PBM and standard treatment groups regarding xerostomia, trismus, analgesic use, or oral candidiasis incidence.

Conclusion: PBM showed effectiveness in delaying onset and reducing the severity of oral mucositis and hyposalivation, as well as alleviating pain and dysgeusia at critical moments. However, it had no significant impact on xerostomia, trismus, analgesic use, or oral candidiasis.

Introduction

With the increasing prevalence of cancer globally, attention is shifting towards the importance of multidisciplinary care and interventions to prevent and manage the negative effects of cancer therapy [1]. According to the latest estimates from the Global Cancer Observatory, by 2050, the number of new cases of head and neck cancer (H&N) worldwide is expected to increase by 61.6 % (291,009) [2].

H&N treatment is multimodal and includes surgery, radiotherapy (RT) and chemotherapy (CT), either alone or in combination, such as chemoradiotherapy (CRT) [3]. The inflammatory processes resulting from these treatments are responsible for the side effects, which, although undesired, are expected [4]. Acute effects may occur during treatment or in the period immediately following its conclusion [5], including damage to oral mucosa cells (mucositis), taste disorders (dysgeusia), difficulty swallowing (dysphagia), decrease in salivary production (hyposalivation), subjective sensation of dry mouth (xerostomia), and reduced mouth opening (trismus) [4–7], which affect the oral cavity. It is also a moment when patients are more susceptible to opportunistic infections such as oral candidiasis (OC) [5,8]. There are

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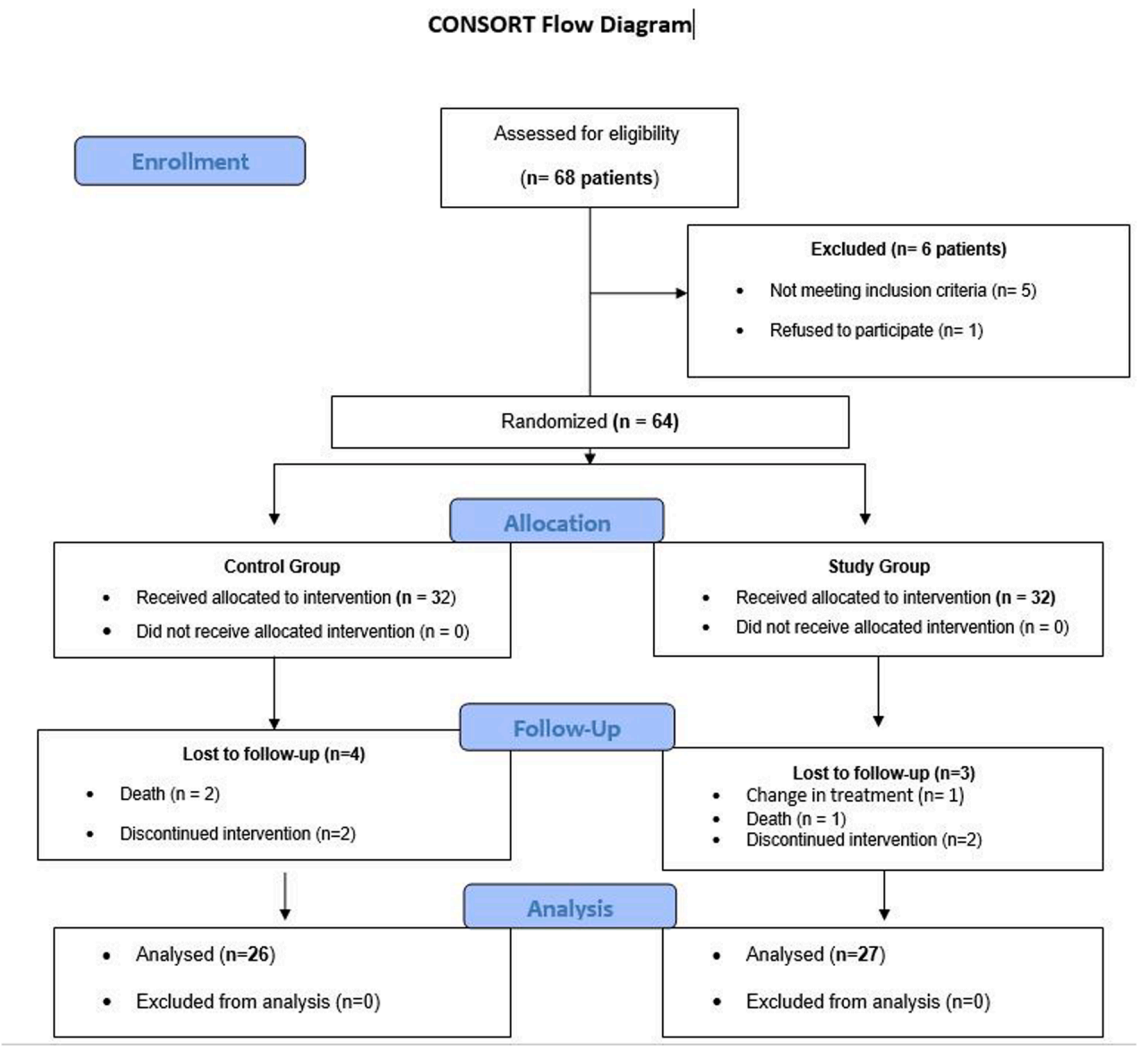

Fig. 1. CONSORT flow chart.

also late effects that may appear months or years after the treatment has ended, such as radiation-induced caries and osteoradionecrosis (ORN), or medication-related osteonecrosis of the jaw (MRONJ) [5].

Oral mucositis (OM) is one of the most frequent and significant side effects [4,9]. It is often associated with unfavourable outcomes, since the debilitating discomfort and dysfunction due to the pain it causes can be reflected in delays and/or termination of cancer treatment, as well as unable to eat soft food or requires support parenteral feeding [4,10]. In addition to the negative impact of the life quality of patients [11], these events contribute to increased treatment costs due to hospital stays, nutritional support and the administration of drugs such as opioids, anti-inflammatories and antimicrobials [4,9,12].

To date, there are no known pharmacological or non-pharmacological treatments that can completely prevent the occurrence of this effects [4,11,13]. Several measures for the OM prevention and treatment are recommended in the MASCC/ISOO guidelines (Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology), among which, the photobiomodulation therapy (PBM), with scientific evidence level I [14]. By increasing cellular metabolism, PBM acts accelerating tissue repair, modulating inflammation and reducing painful symptoms [9,15]. Additionally, it is a safe and minimally invasive therapeutic modality that adheres principles of supportive care for oncology patients, effectively preventing and treating secondary complications of antineoplastic therapy [15–18]. Although the role of PBM in OM mitigation is well established [14,19], there is a considerable variability in laser parameters and equipment, which makes the standardisation of protocols difficult [20,21]. Therefore, we conducted this study in line with the recent recommendations [14,20], with the aim of measuring the effect of PBM application in the OM prevention and treatment, and secondarily, on other functional and subjective manifestations such as hyposalivation, trismus, xerostomia, treatment-related pain and dysgeusia. We hope that the study will contribute to the optimisation of clinical protocols for a better evaluation of results.

Material and methods

A randomised, single-blind clinical trial was conducted comparing two independent groups: a control group (CG) and a study group (SG), in a single centre, the University Hospital Complex (CHUS) of Santiago de Compostela, Spain. Patients were recruited and seen during the follow-up. Invitations to participate were issued by their responsible physicians (AGC and CVF). Once the H&N neoplasia was diagnosed and confirmed, and while the study was in the recruitment period, all CHUS patients were offered the opportunity to participate in the study. Recruitment ran from March 2020 to the end of October 2022. The study had the ethical approval of the Regional Research Ethics Committee of Santiago - Lugo (Ref. 2021/262) and followed the ethical principles of the Declaration of Helsinki and CONSORT checklist [22,23]. The study is also registered in the International Clinical Trials Registry Platform (ClinicalTrials.com)

Table 1
Clinical features and descriptive statistics comparison Control Group (CG) vs. Study Group (SG).

		CG (n = 26) n patients (%)	SG (n = 27) n patients (%)	*Total* (n = 53) n patients (%)	*p*-value*
Age (years)	Mean (range)	62.7 (42–79)	65.8 (43–85)	64.3 (42–85)	0.288
Gender	Male	19 (73.1)	17 (63)	36 (67.9)	0.440
	Female	7 (26.9)	10 (37)	17 (32.1)	
Smoking	Never	6 (23.1)	10 (37)	16 (30.2)	0.735
	Smoker	10 (38.5)	5 (18.5)	15 (28.3)	
	Smoking cessation	10 (38.5)	12 (44.4)	22 (41.5)	
	Smoking load (cigarettes/day) Mean ± SD	20.5 ± 12	13.1 ± 12.6	–	0.033*
	Years smoking (Mean ± SD)	29.5 ± 19.1	25.6 ± 21.3	–	0.482
Alcohol	No	2 (7.7)	8 (29.6)	10 (18.9)	0.094
	Yes—active use	20 (76.9)	16 (59.3)	36 (67.9)	
	Yes—alcohol withdrawal	4 (15.4)	3 (11.1)	7 (13.2)	
	Years alcohol consumption (Mean ± SD)	35.2 ± 14.8	25.6 ± 18.7	–	0.044*
Primary Tumour site	Oral cavity	3 (11.5)	8 (29.6)	11 (20.8)	0.304
	Oropharynx	17 (65.4)	13 (48.1)	30 (56.6)	
	Nasopharynx	6 (23.1)	6 (22.2)	12 (22.6)	
T-Stage	T1	2 (7.7)	2 (7.4)	4 (7.5)	0.319
	T2	5 (19.2)	12 (44.4)	17 (32.1)	
	T3	12 (46.2)	6 (22.2)	18 (34)	
	T4	7 (26.9)	7 (25.9)	14 (26.4)	
N-Stage	N0	0 (0)	3 (11.1)	3 (5.7)	0.757
	N1	9 (34.6)	5 (18.5)	14 (26.4)	
	N2	13 (50)	15 (55.6)	28 (52.8)	
	N3	4 (15.4)	4 (14.8)	8 (15.1)	
M−Stage	Mx	1 (3.8)	0 (0)	34 (64.2)	0.541
	M0	16 (61.5)	18 (66.7)	18 (34)	
	M1	9 (34.5)	9 (33.3)	1 (1.9)	
Clinical Cancer Stage	II	2 (7.7)	5 (18.5)	7 (13.2)	0.652
	III	15 (57.7)	12 (44.4)	27 (50.9)	
	IV	9 (34.6)	10 (37)	19 (35.8)	
Treatment	RT only	4 (15.4)	6 (22.2)	10 (18.9)	0.756
	CRT**	18 (69.2)	14 (51.9)	32 (60.4)	
	Surgery + RT	2 (7.7)	4 (14.8)	6 (11.3)	
	Surgery + CRT**	2 (7.7)	3 (11.1)	5 (9.4)	
RT dose	60 – 70 Gy	2 (7.7)	7 (25.9)	9 (17)	0.078
	>70 Gy	24 (92.3)	20 (74.1)	44 (83)	
CT sessions	None	6 (23.1)	10 (37)	16 (30.2)	0.386
	3	19 (73.1)	15 (55.6)	34 (64.2)	
	5	1 (3.8)	2 (7.4)	3 (5.7)	
Hygiene	Grade 0	10 (38.5)	8 (29.6)	18 (34)	
	Grade 1	4 (15.4)	9 (33.3)	13 (24.5)	0.600
	Grade 2	6 (23.1)	8 (29.6)	14 (26.4)	
	Grade 3	6 (23.1)	2 (7.4)	8 (15.1)	

* When the *p*-value was statistically significant. RT = Radiotherapy; CRT = Chemoradiotherapy; Gy = Gray; SD = Standard Deviation.

under the identifier NCT04717765.

All patients included in this study met the inclusion criteria: (1) over 18 years old; (2) had a diagnosed and histologically confirmed cancer (3) in the oral cavity, oropharynx, or nasopharynx region; (4) had signed the informed consent form before any study-related intervention was performed; (5) when surgical or nonsurgical treatment included exclusive RT or CRT.

Exclusion criteria were: (1) previous antineoplastic treatment in any region and stage; (2) patients scheduled to receive palliative RT; (3) or those enrolled in another research trial to monitor side effects of antineoplastic treatment; (4) who chose not to undergo the proposed dental treatment protocols for oral cavity adaptation; (5) or did not accept daily use of 0.12 % chlorhexidine; (6) and/or missed three or more consecutive PBM sessions (in the intervention group); (7) who decided to withdraw from the study at any stage; (8) and finally, death during any follow-up period.

Sample size calculation

The following statistical criteria were established: an effect size corresponding to an increase or decrease in the expected OM grade of at least 1 point in the second week of treatment; considering a standard deviation of 1.8; an alpha error of 0.05; and a statistical power of 90 %. Once these criteria were met, the variance test for independent samples was applied. It was determined that a sample of 26 patients would be required in each group (52 in total), considering an estimated loss of 10 %. The final sample size was 53 patients. The G Power 3.1.5 programme was used for the calculation.

Randomisation and Masking

Patients were randomly assigned to one of the treatment groups using a randomisation scheme generated by the SAS programme (version 8.02). Two block lists of four patients each were created, according to a 1:1 ratio. Due to the open-label design of the study, treatment was not masked to participants or the personnel responsible for administering PBM. However, the evaluators were blinded to the degree of OM (IBPP) and to the handling and assessment of data (MPS).

Study variables

All patients who met the inclusion criteria were fully informed of the characteristics of the study and invited to participate. Those who accepted were assessed for demographic data, including gender, age, habits, tobacco use, alcohol consumption, and oral hygiene level. In addition, clinical variables such as disease stage, tumour location and stage (AJCC 8th edition), TNM classification [24] and antineoplastic treatment protocols were collected. Additionally, all patients underwent a comprehensive clinical and oral evaluation, including a panoramic dental radiography, before initiating antineoplastic treatment. They were provided with an oral care protocol, including dental treatment when necessary (scaling, filling, extraction), and instructions on oral care during antineoplastic treatment [25].

Intervention

Patients in both groups received the standard care protocol, including analgesics (tablets and/or patches), local anaesthetics (lidocaine mouthwash), nutritional support with oral supplements, and speech therapy support.

Furthermore, patients assigned to the SG received PBM during antineoplastic treatment, both preventively and therapeutically, while

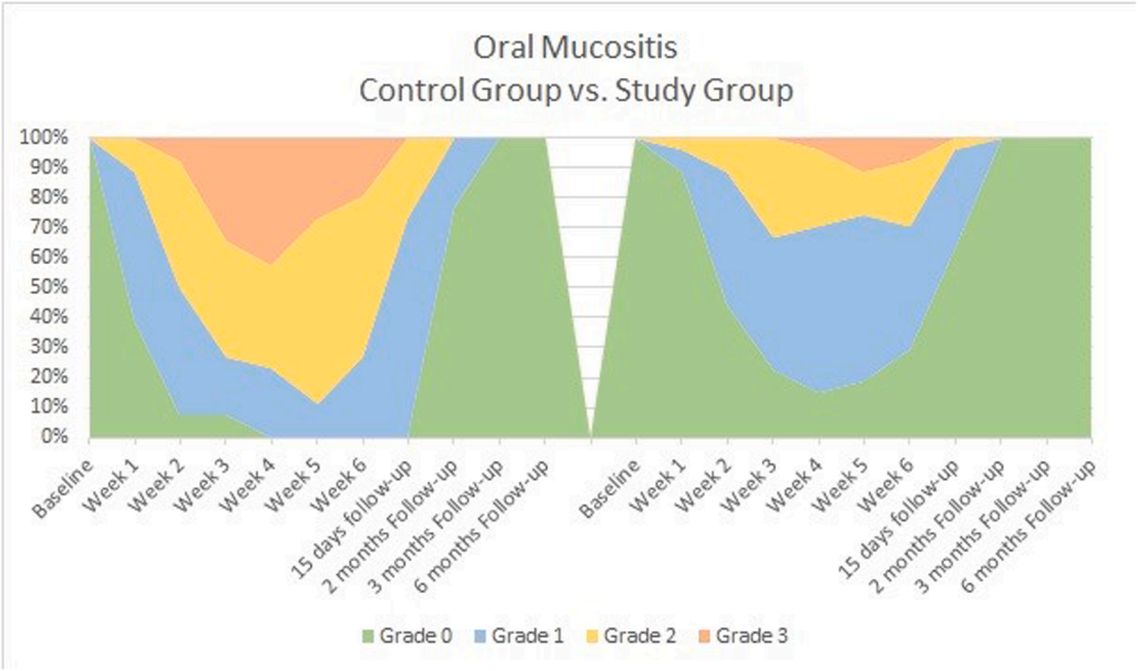

Fig. 2. Graphic of the variation of assessment of outcome OM over the time of treatment and follow-up.

those in the CG received 0.12 % chlorhexidine mouth rinses, three times a day, for one minute.

Assessments

Baseline assessment was performed prior to starting the antineoplastic treatment, usually during the appointment with the oral medicine unit of the dental faculty at USC, for oral environment adaptation. Subsequent weekly assessments were performed in a consultation with the nursing service in the radiology unit of CHUS. The assessment protocol included six sessions, one per week, during antineoplastic treatment, and the follow-up protocol included 4 sessions, at 15 days, 2, 3, and 6 months after completion of the antineoplastic treatment (Supplementary 1). The clinical assessment was always performed by the same dentist (IBPP), by intraoral and extraoral examination.

Measurement of primary and secondary outcomes

The primary outcome is to assess the presence and severity of OM in both groups. Secondary outcomes included the severity of pain and dysgeusia, analgesic use, hyposalivation, xerostomia, trismus, and candidiasis. In addition, data on the degree of radiodermatitis and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core Module (QLQ-C30), and Head and Neck Module (QLQ-H&N35) were collected but will not be evaluated in this study.

OM assessment

During the clinical evaluation, the presence of OM was assessed dichotomously (yes/no), as well as its severity, rated from 0 to 4, as proposed by the World Health Organization (WHO) [26].

Pain and dysgeusia assessment

The assessment of pain and dysgeusia relied on self-reported subjective analysis. Using the Visual Analogue Scale (VAS), ratings ranging from 0 to 10 were obtained (0 – no pain/dysgeusia, 10 – worst possible pain/dysgeusia). For a better result analysis, when necessary, ranges were classified as: 1–3 mild, 4–6 moderate, 7–10 severe.

Analgesic use assessment

During each assessment, patients were asked about the use of analgesics, and their response was recorded dichotomously (yes/no).

Salivary assessment

The occurrence of hyposalivation was verified with the unstimulated (GST I) and stimulated (GST II) global saliva tests. Using an absorbent paper strip with a millimetre scale (mm), the modified Schirmer test was performed [27,28]. Patients were instructed not to eat or drink anything for one hour before each visit at which GST was measured. For a better result analysis, in some cases, the mean was considered in mm/5min, while in other times evaluations were established as follows: $<$ 30 mm/5min – extreme hyposalivation, 30 to 36.99 mm/5min – mild hyposalivation, and $\geq$37 mm/5min – normal salivation, for GST I; and $<$50 mm/5min – glandular hypofunction or $\geq$50 mm/5min – normal glandular function, for GST II [28].

Xerostomia assessment

Patients were provided with the validated Spanish version of the Xerostomia Inventory (XI) questionnaire (XI-Sp) [29]. It is a subjective scale composed of 11 items (measured on a Likert scale), divided into five categories, which classifies xerostomia on a severity score from 11 to 55; the higher the final score, the more severe the xerostomia [30]. Again, when necessary, for better result analysis, ranges were established: 11–21 no xerostomia, 22–32 mild xerostomia, 33–43 moderate xerostomia, and 44–55 severe xerostomia.

Trismus assessment

Mouth opening was measured by placing a calliper ruler between the edge of the right upper central incisor and the edge of the right lower central incisor (in dentate patients), or at the points on the alveolar ridges corresponding to the former location (in edentulous patients). Mouth opening was recorded in millimetres (mm). For the analysis of results, the measurement in mm was considered, or a dichotomous evaluation (yes/no) was established, with "yes" indicating a mouth opening of $\leq$35 mm [31].

OC assessment

The evaluation was based on a clinical examination of the oral

Table 2
Mean grade of mucositis, pain and dysgeusia assessment per week, in the baseline period and during 6 weeks of treatment, and the follow-up period.

	Toxicities	Mucositis Grade		Pain VAS		Dysgeusia VAS	
Time	**Measures**	**Mean ± SD**	***p*-value***	**Mean ± SD**	***p*-value***	**Mean ± SD**	***p*-value***
	Group						
Baseline	Control	0.0 ± 0.0	1.000	1.5 ± 2.1	0.243	0.4 ± 1.3	0.161
	Study	0.0 ± 0.0		2.3 ± 2.6		0.7 ± 1.3	
Week 1	Control	0.7 ± 0.6	0.000*	3.2 ± 2.5	0.720	3.5 ± 2.5	0.413
	Study	0.1 ± 0.4		3.4 ± 2.2		3.1 ± 2.7	
Week 2	Control	1.5 ± 0.7	0.000*	4.5 ± 2.3	0.570[T]	5.0 ± 2.1	0.341
	Study	0.6 ± 0.6		4.9 ± 2.5		4.8 ± 2.8	
Week 3	Control	2.0 ± 0.9	0.001*	6.3 ± 2.3	0.160	6.5 ± 2.3	0.064
	Study	1.1 ± 0.7		5.4 ± 2.4		5.4 ± 2.7	
Week 4	Control	2.1 ± 0.8	0.000*	6.7 ± 1.9	0.247	6.7 ± 2.3	0.199
	Study	1.1 ± 0.7		6.0 ± 2.6		5.9 ± 2.5	
Week 5	Control	2.1 ± 0.6	0.000*	7.2 ± 1.8	0.048*	7.6 ± 2.0	0.068
	Study	1.1 ± 0.8		6.0 ± 2.4		6.3 ± 2.4	
Week 6	Control	1.9 ± 0.6	0.001*	7.2 ± 2.1	0.067	7.9 ± 2.0	0.034*
	Study	1.0 ± 0.9		5.9 ± 2.6		6.3 ± 2.8	
15 days Follow-up	Control	1.2 ± 0.4	0.000*	5.6 ± 2.6	0.049*[T]	6.8 ± 2.3	0.039*
	Study	0.4 ± 0.5		4.3 ± 2.3		5.4 ± 2.5	
2 months Follow-up	Control	0.2 ± 0.4	0.009*	2.9 ± 2.2	0.454	4.6 ± 2.2	0.323
	Study	0.0 ± 0.0		2.4 ± 2.1		4.2 ± 2.8	
3 months Follow-up	Control	0.0 ± 0.0	1.000	1.5 ± 1.8	0.539	3.1 ± 2.9	0.695
	Study	0.0 ± 0.0		1.3 ± 1.7		2.7 ± 2.2	
6 months Follow-up	Control	0.0 ± 0.0	1.000	0.4 ± 0.9	0.527	1.8 ± 1.9	0.575
	Study	0.0 ± 0.0		0.6 ± 1.2		1.6 ± 2.2	

Note: *Student's t*-test were reported when it was possible [(T)], but most group comparisons were made using the *Mann-Whitney* test.
* When the *p*-value was statistically significant. SD = standard deviation; VAS = visual analogue scale.

mucosa. A positive analysis for Candida infection was considered upon identifying any clinical variant (pseudomembranous, erythematous, hyperplastic), with suspicion recorded dichotomously (yes/no). In cases of positive clinical evaluation, the diagnosis was confirmed by sampling the dorsum of the tongue and buccal mucosa with swabs, followed by cytological examination [32].

All pharmacological prescriptions, including analgesics, anti-inflammatory drugs, antifungals, and local anaesthetics, were made by the medical team responsible for routine care and were therefore blinded to the study group assignment. All data collected during treatment and follow-up were recorded in an Excel file (IBPP), and subsequently subjected to statistical analysis (MPS).

PBM application protocol

The patients in the SG received intraoral and some extraoral PBM applications approximately 30 min before or after the daily fraction of RT. Sessions were performed daily, five times a week (Monday to Friday), throughout the course of RT. Each PBM session was performed using the same diode laser device (Laser Duo, MMOptics Ltda., São Carlos, Brazil) and by the same trained dentist (GCVC). The laser device emits red (660 nm) and infrared (808 nm) light continuously, at a power of 100 mW, with a spot diameter of 0.03 cm^2, delivering a dose of 0.1 Joule/second (J/s.) per point (p/p).

In each session, the following application was administered: intraoral, using a red laser, at least 78 points (depending on the size of each patient's oral cavity) were distributed along the right and left oral mucosa, bilateral labial commissures, inner upper and lower lip, on the ventral, dorsal and lingual surfaces of the tongue, bilateral hard and soft palate (including tonsillar pillars and uvula) and retromolar area. The application was performed with continuous laser emission and in contact with the mucosa whenever possible, for 10 s (1 J) per point; extraoral, using an infrared laser, 10 points were applied, three on each parotid gland and two on each submandibular gland, perpendicular and in contact with the skin, for 20 s (2 J) per point. Further specifications of the laser device and protocol used in the clinical study are given in Supplementary 2.

PBM was not administered over an active tumour site. In cases where the patient had not undergone surgical resection of the tumour prior to RT, the protocol was adapted so that PBM was only applied to the healthy region. In all the sessions, patient, and operator, wore safety goggles suitable for each wavelength used. For infection control purposes, a systematic disinfection routine with 70 % ethyl alcohol was performed before and after each session, and a disposable plastic film was used to protect the device.

Table 3
The OR for the risk of developing mucositis was calculated by covariate and treatment group versus OM clinical presence. The statistical analysis for the univariate OR was performed using univariate multinomial logistic regression analysis. The statistical analysis for the adjusted OR was performed using gradual multivariate multinomial logistic regression adjusted for gender, age, clinical stage of cancer, cancer treatment and intervention group.

Time	Covariate vs. oral mucositis				
		Univariate OR (95 % CI)	*p* value	Multivariate OR (95 % CI)	*p* value
Week 1	Gender	1.527 (0.442 – 5.277)	0.503	1.553 (0.288 – 8.360)	0.608
	Years old	1.002 (0.950—1.058)	0.928	1.029 (0952 – 1.114)	0.468
	Clinical Stage of Cancer				
	Stage I vs. Stage III	0.867 (0.129 – 5.817)	0.883	2.459 (0.207 – 29.165)	0.476
	Stage I vs. Stage IV	1.490 (0.433 – 5.121)	0.527	1.349 (0.284 – 6.410)	0.706
	Cancer Treatment				
	RT only vs. CRT	2.667 (0.212 – 33.486)	0.447	3.652 (0.167 – 80.119)	0.411
	RT only vs. Surgery + RT	2.400 (0.239 – 24.063)	0.457	1.010 (0.129 – 31.426)	0.619
	RT only vs. Surgery + CRT	2.000 (0.125 – 31.975)	0.624	3.395 (0.102 – 113.442)	0.495
	Intervention group	12.800 (3.042—53.860)	0.001*	18.385 (3.249—104.025)	0.001*
Week 2	Gender	0.267 (0.052—1.361)	0.112	0.080 (0.009 – 0706)	0.023*
	Years old	0.991 (0.934—1.052)	0.769	0.969 (0.883 – 1.061	0.485
	Clinical Stage of Cancer				
	Stage II vs. Stage III	0.893 (0.129 – 6.162)	0.908	0.899 (0.067 – 11.988)	0.936
	Stage II vs. Stage IV	1.020 (0.268 – 3.879)	0.976	0.849 (0.135 – 5.355)	0.862
	Cancer Treatment				
	RT only vs. CRT	6.000 (0.563 – 63.984)	0.138	34.355 (1.296 – 910.461)	0.034*
	RT only vs Surgery + RT	4.500 (0.634 – 31.946)	0.133	4.631 (0.355 – 60.479)	0.242
	RT only vs. Surgery + CRT	7.500 (0.458 – 122.696)	0.158	11.427 (0.269 – 484.699)	0.203
	Intervention group	9.600 (1.881 – 48.999)	0.007*	27.38 (3.282—228.56)	0.002*
Week 3	Gender	0.667 (0.120 – 3.709)	0.643	0.413 (0.059 – 2.884)	0.372
	Years old	0.977 (0.906 – 1.053)	0.541	0.962 (0.876 – 1.056)	0.411
	Clinical Stage of Cancer				
	Stage II vs. Stage III	1.600 (0.147 – 17.411)	0.700	2.090 (0.143—30.479)	0.590
	Stage II vs. Stage IV	2.133 (0.418 – 10.889)	0.362	2.433 (0.400 – 14.797)	0.334
	Cancer Treatment				
	RT only vs. CRT	2.250 (0.111 – 45.723)	0.598	3.145 (0.113 – 87.230)	0.499
	RT only vs. Surgery + RT	1.350 (0.124 – 14.734)	0.806	0.717 (0.054 – 9.448)	0.800
	RT only vs. Surgery + CRT	1.250 (0.058 – 26.869)	0.887	1.739 (0.053 – 57.531)	0.757
	Intervention group	3.429 (0.624 – 18.845)	0.156	4.542 (0.679 – 30.382)	0.119

* When the *p*-value was statistically significant. OR = Odds Ratio; CI = confidence interval; RT = Radiotherapy; CRT = Chemoradiotherapy.

Statistical analysis

Analysis of data regarding demographic characteristics, clinical-pathological features and clinical outcomes collected during the pre-treatment period (baseline) was performed using descriptive statistical calculations based on mean, median, standard deviation and proportion values. Analysis of primary and secondary outcome variables involved comparisons between the two groups (CG vs. SG), including calculation of measures of central tendency (mean) and dispersion (SD) for quantitative variables, and frequency distributions (%) for qualitative variables. Univariate analysis for independent samples was performed using *Student's t*-test (parametric) or the *Mann-Whitney U* test (non-parametric) when the assumption of normal distribution was not met as assess by the *Kolmogorov-Smirnov* test.

To verify the frequency of occurrence of the variable of interest, the *Chi*-square test or *Fisher's* exact test was applied. Using sequential multinomial logistic regression analysis for the study variables, *odds* ratio (OR) was calculated, when possible, for OM, GST I and II. Repeated measures analysis of variance was performed for the outcomes dysgeusia, GST I and II, and xerostomia, using ANOVA or *Friedman* test (non-parametric). Time was considered as the repeated measure and study group as the independent variable. The level of significance adopted was for *p*-values ≤ 0.05. The data obtained in the study were statistically analysed using the *Jamovi* (2024) v. 2.5.

Results

Clinical and pathological findings

A total of 64 patients were randomised from February 2020 to the end of October 2022. Eleven patients were excluded during treatment (CG = 6, SG = 5). A total of 53 patients completed their participation in the study and were included in the analysis (CG = 26, SG = 27). The reasons for exclusion are described in the flowchart in Fig. 1.

During the baseline period, patients in the control and PBM groups had similar clinical and pathological characteristics (Table 1). The majority of patients in both groups were male (73.1 % vs. 63 %), with a history of tobacco and alcohol use. The oropharynx was the most frequent primary tumour site (65.4 % vs. 48.1 %), and CRT was the most common cancer treatment (69.2 % vs. 51.1 %). No statistically significant differences were observed in the clinical and pathological characteristics between the two groups.

Oral mucositis

In the weekly comparison according to the WHO scale, progression was significantly faster in the CG (Fig. 2), which, from week 1 ($p < 0.001$) and throughout the follow-up period up to 2 months, had a significantly higher mean OM grade compared to the SG. At both the 3 and at the 6 months follow-up, the prevalence of OM was zero in both groups (Table 2).

Logistic regression confirmed that not receiving PBM, that is, being

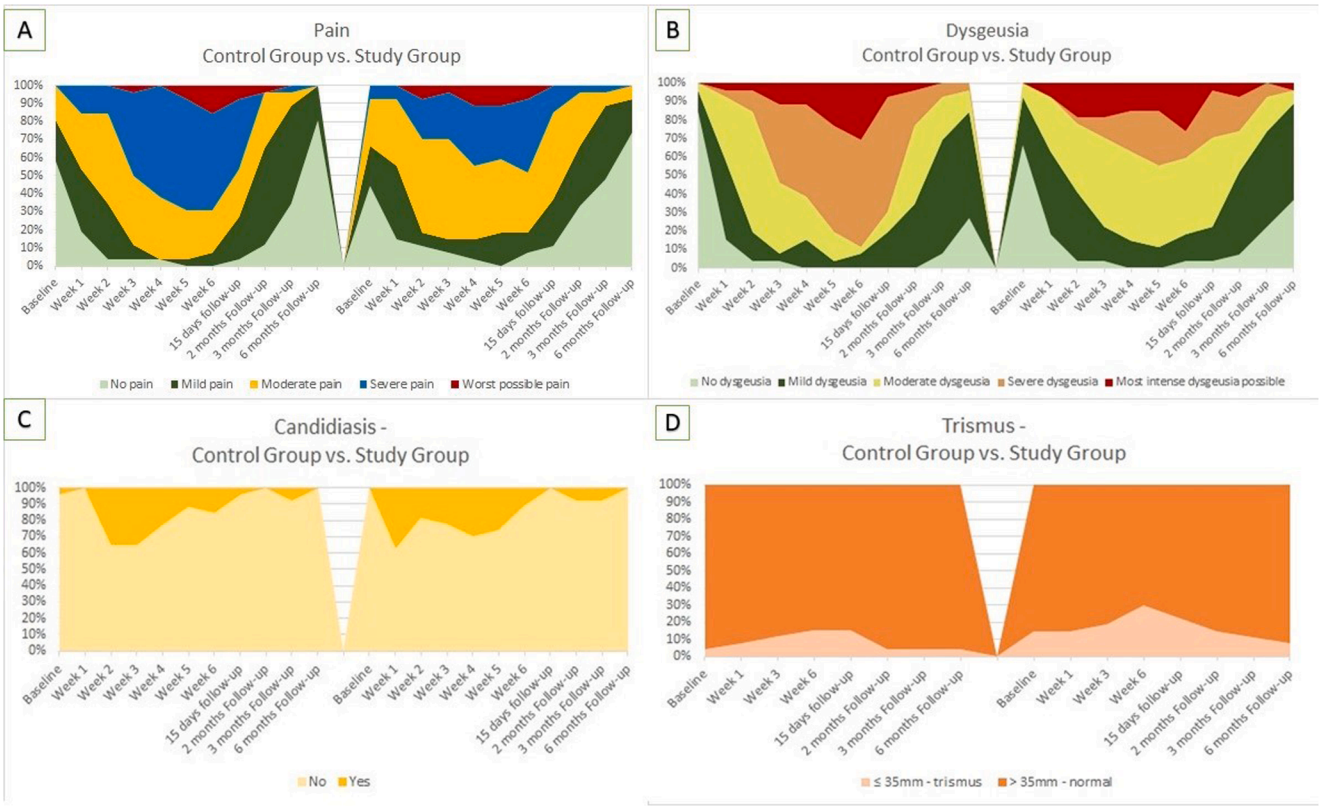

Fig. 3. Graphic of the variation of assessment of outcomes over the time of treatment and follow-up. **3a.** Pain and **3b.** Dysgeusia **3c.** Candidiasis **3d.** Trismus.

in the CG, resulted in an OR of 12.800 times greater for developing OM already in the first week of treatment (95 % CI 3.042 – 53.860; p = 0.001). Furthermore, the role of variables such as age, gender, clinical tumour stage and anticancer treatment in the development of OM was assessed separately, none of which yielded significant results. However, when all variables were incorporated into the model, a higher OR of 16.683 (95 % CI 3.244 – 85.803; p = 0.001) was observed for the development of OM when not receiving PBM. This risk is even more pronounced in week 2 (Table 3).

Pain and analgesia

From week 3 to the 3-month follow-up, the mean pain score was lower in the SG, although a significant difference was only observed at week 5 and at the 15-day follow-up ($p < 0.05$). The highest mean pain score occurred at week 5 in both groups, with 7.2 ± 1.8 for the CG and 6.0 ± 2.4 for the SG, $p < 0.05$ (Table 2). A graph was constructed to facilitate visualisation of the evolution of pain in both groups throughout treatment (Fig. 3.a; Supplementary 3).

In terms of analgesic use, the groups showed a similar proportion, except at 2-month follow-up, where there was a significantly lower difference in analgesic consumption in the CG ($p < 0.05$) (Table 4 and Fig. 3b).

Dysgeusia

All patients included in the study reported taste alteration perception during the treatment. Weekly evaluations showed a continuous progression in the severity of dysgeusia in both groups, although from the first week of follow-up, SG patients already had a lower mean score compared to CG, with statistically significant differences only occurring at the last week of treatment (week 6) and at the 15-day follow-up ($p < 0.05$) (Table 2). Fig. 3b shows the evolution of dysgeusia in both groups throughout treatment and follow-up. Analysis of variance was performed comparing measurements over time between the two groups independently (Table 5).

Hyposalivation and xerostomia

The mean values of GST I in the group receiving PBM were higher than the mean values of the CG at all times when this variable was evaluated. The results were statistically significant from week 1 to the 6-month follow-up (Table 6). The lowest means were observed at 15-day follow-up in both groups, 22.15 ± 13.34 CG and 34.30 ± 12.41 SG, ($p < 0.001$). Logistic regression confirmed that patients in the CG had an OR of 19.125 for "mild hyposalivation" and 6.906 for "extreme hyposalivation" already in the first week of treatment, IC95% 1.702 – 28.026; $p < 0.05$ and IC95% 2.919–125.319; $p < 0.005$, respectively (Table 7).

Regarding the SGT II tests, the CG showed a stable mean score from the first week to the 6-month follow-up, with its lowest value at 2-month follow-up (39.85 ± 23.27). After starting with a mean of 57.70 ± 21.38 at baseline, it decreased to 44.30 ± 15.53 at week 3, and then remained stable until the 3-month follow-up. The SG also showed a stable mean score (Table 6). At the final follow-up (6 months), the SG showed an improvement in the mean score, resulting in a statistically significant difference between the groups (p = 0.001). The CG concluded follow-up with an OR of 6.875 for "glandular hyposalivation," 95 % CI 1.858 – 25.432; $p < 0.005$ (Table 7).

For xerostomia, the means were similar in both groups throughout the study, with a mean XI score of 28.82 ± 8.94 for the CG and 31.78 ± 9.23 for the SG.

Fig. 4 illustrates the variation in SGT I, SGT II and xerostomia measures throughout the treatment. Analysis of variance was also performed, comparing the measures within the same group independently over time (Table 5).

Table 4
Chi^2 and *p*-value to dichotomic evaluation (yes / no) for Candidiasis, Analgesic use, Mucositis, Trismus and Salivary Global Test II (GST II), Control Group vs. Study Group.

	Outcome	Candidiasis			Analgesics			Mucositis			Trismus			GST II		
Time	Group	n (%)		*p*-value	n (%)		*p*-value	n (%)		*p*-value	n (%)		*p*-value	n (%)		*p*-value
		No	Yes		No	Yes		No	Yes		No	Yes		No	Yes	
Baseline	**Control**	25 (96.5)	1 (3.9)	0.491	20 (76.9)	6 (23.1)	0.101	26 (100)	0 (0)	–	25 (96.2)	1 (3.8)	0.351	13 (50)	13 (50)	0.035*
	Study	27 (100)	0 (0)		15 (55.6)	12 (44.4)		27 (100)	0 (0)		23 (85.2)	4 (14.8)		6 (22.2)	21 (77.8)	
Week 1	**Control**	26 (100)	0 (0)	0.001*	15 (57.7)	11 (42.3)	0.669	10 (38.5)	16 (61.5)	0.000*	24 (92.3)	2 (7.7)	0.669	19 (73.1)	7 (26.9)	0.008*
	Study	17 (62.9)	10 (37)		14 (51.9)	13 (48.1)		24 (88.9)	3 (11.1)		23 (85.2)	4 (14.8)		10 (37)	17 (63)	
Week 2	**Control**	17 (65.4)	9 (34.6)	0.224	11 (42.3)	15 (46.9)	0.695	2 (7.7)	24 (92.3)	0.002*						
	Study	22 (81.4)	5 (18.5)		10 (37)	17 (63)		12 (44.4)	15 (55.6)							
Week 3	**Control**	17 (65.4)	9 (34.6)	0.372	7 (26.9)	19 (73.1)	0.691	2 (7.7)	24 (92.3)	0.250	23 (88.5)	3 (11.5)	0.704	20 (76.9)	6 (23.1)	0.268
	Study	21 (77.7)	6 (22.2)		6 (22.2)	21 (77.8)		6 (22.2)	21 (77.8)		22 (81.5)	5 (18.5)		17 (63)	10 (37)	
Week 4	**Control**	20 (76.9)	6 (23.1)	0.757	6 (23.1)	20 (76.9)	0.941	0 (0)	26 (100)	0.111						
	Study	19 (70.3)	8 (29.6)		6 (22.2)	21 (77.8)		4 (14.8)	23 (85.2)							
Week 5	**Control**	23 (88.5)	3 (11.5)		4 (15.4)	22 (84.6)	0.525	0 (0)	26 (100)	0.051						
	Study	20 (74)	7 (25.9)	0.293	6 (22.2)	21 (77.8)		5 (18.5)	22 (81.5)							
Week 6	**Control**	22 (84.6)	4 (15.4)		3 (11.5)	23 (88.5)	0.478	0 (0)	26 (100)	0.004*	22 (84.6)	4 (15.4)	0.215	20 (76.9)	6 (23.1)	0.589
	Study	24 (88.8)	3 (11.1)	0.704	5 (18.5)	22 (81.5)		8 (29.6)	19 (70.4)		19 (70.4)	8 (29.6)		19 (70.4)	8 (29.6)	
15 days Follow-up	**Control**	25 (96.5)	1 (3.9)		8 (30.8)	18 (69.2)	0.630	0 (0)	26 (100)	0.000*	22 (84.6)	4 (15.4)	0.525	20 (76.9)	6 (23.1)	0.810
	Study	27(100)	0 (0)	0.491	10 (37)	17 (63)		17 (63)	10 (37)		21 (77.8)	6 (22.2)		20 (74.1)	7 (25.9)	
2 months Follow-up	**Control**	26 (100)	0 (0)		21 (80.8)	5 (19.2)	0.026*	20 (76.9)	6 (23.1)	0.010*	25(96.2)	1 (3.8)	0.351	21 (80.8)	5 (19.2)	0.049*
	Study	25 (92.5)	2 (7.4)	0.491	14 (51.9)	13 (48.1)		27 (100)	0 (0)		23 (85.2)	4 (14.8)		15 (55.6)	12 (44.4)	
3 months Follow-up	**Control**	24 (88.8)	2 (7.6)		23 (88.5)	3 (11.5)	0.181	26 (100)	0 (0)	–	25(96.2)	1 (3.8)	0.610	20 (76.9)	6 (23.1)	0.268
	Study	25 (92.5)	2 (7.4)	1.000	20 (74.1)	7 (25.9)		27 (100)	0 (0)		24 (88.9)	3 (11.1)		17 (63)	10 (37)	
6 months Follow-up	**Control**	26 (100)	0 (0)		23 (88.5)	3 (11.5)	1.000	26 (100)	0 (0)	–	25(96.2)	1 (3.8)	1.000	22 (84.6)	4 (15.4)	0.002*
	Study	27 (100)	0 (0)	–	24 (88.9)	3 (11.1)		27 (100)	0 (0)		25 (92.6)	1 (7.4)		12 (44.4)	15 (55.6)	

* When the *p*-value was statistically significant.

Table 5
Analysis of variance for the outcomes dysgeusia and xerostomia, comparing the results of the same group at different times. * When the *p*-value was statistically significant. MD = mean difference; CI = confidence interval; GST I = no stimulated salivary global test; GST lI = stimulated salivary global test.

Time	Group	Dysgeusia	*p*-value	GST I	*p*-value	GST II	*p*-value	Xerostomia	*p*-value
		MD (IC 95 %)		MD (IC 95 %)		MD (IC 95 %)		MD (IC 95 %)	
Baseline vs. week 3	Control	− 6.077 (− 8.132, − 4.022)	0.000*	11.808 (− 6.832, 30.448)	1.000	10.692 (− 13.066, 34.451)	1.000	− 13.885 (− 18.564, − 9.206)	0.000*
	Study	− 4.704 (− 7.049, − 2.358)	0.000*	9.037 (− 1.128, 19.202)	0.131	13.407 (− 0.830, 25.984)	0.028*	− 10.630 (− 17.811, − 3.448)	0.001*
Baseline vs. week 6	Control	− 7.462 (− 9.721, − 5.202)	0.000*	17.538 (3.220, 31.857)	0.007*	11.846 (− 11.858, 35.550)	1.000	− 17.538 (− 22.398, − 12.679)	0.000*
	Study	− 5.556 (− 7.846, − 3.266)	0.000*	8.852 (− 2.931, 20.635)	0.411	12.630 (− 1.541, 26.801)	0.129	− 12.630 (− 19.311, − 5.948)	0.000*
Baseline vs. 3 months	Control	− 2.731 (− 5.240, − 0.221)	0.021*	19.154 (3.612, 34.695)	0.006*	12.423 (− 6.020, 30.867)	0.748	− 8.538 (− 13.132, − 3.945)	0.000*
	Study	− 1.926 (− 3.644, − 0.208)	0.015*	7.148 (− 4.379, 18.675)	1.000	10.778 (− 2.563, 24.119)	0.259	− 9.296 (− 15.857, − 2.735)	0.001*
Baseline vs. 6 months	Control	− 1.346 (− 3.079, 0.387)	0.400	13.154 (− 1.753, 28.061)	0.138	12.654 (− 4.377, 29.684)	0.435	− 4.962 (− 9.657, − 0.266)	0.030*
	Study	− 0.889 (− 2.870, 1.093)	1.000	3.148 (− 6.139, 15.769)	1.000	5.889 (− 5.999, 17.776)	1.000	− 7.630 (− 13.865, − 1.394)	0.007*
Week 3 vs. week 6	Control	− 1.385 (− 2.689, − 0.080)	0.028*	5.731 (− 5.315, 16.777)	1.000	1.154 (− 12.593, 14.901)	1.000	− 3.654 (− 6.695, − 0.613)	0.008*
	Study	− 0.852 (− 2.532, 0.828)	1.000	− 0.185 (− 6.111, 5.741)	1.000	− 0.778 (− 8.785, 7.229)	1.000	− 2.000 (− 5.490, 1.490)	1.000
Week 3 vs. 3 months	Control	3.346 (0.570, 6.122)	0.007*	7.346 (− 6.114, 20.806)	1.000	1.731 (− 18.796, 22.257)	1.000	5.346 (0.701, 9.991)	0.013*
	Study	2.778 (0.976, 4.580)	0.000*	− 1.889 (− 10.295, 6.517)	1.000	−2.630 (− 12.774, 7.515)	1.000	1.333 (− 2.967, 5.633)	1.000
Week 3 vs. 6 months	Control	4.731 (2.669, 6.792)	0.000*	1.346 (−10.821, 13.514)	1.000	1.962 (− 15.139, 19.062)	1.000	8.923 (4.007, − 13.839)	0.000*
	Study	3.815 (1.898, 5.732)	0.000*	− 4.222 (− 13.888, 5.444)	1.000	− 7.519 (− 19.188, 4.151)	0.944	3.000 (−1.576, 7.576)	0.867
Week 6 vs. 3 months	Control	4.731 (2.420, 7.041)	0.000*	1.615 (− 7.653, 10.884)	1.000	0.577 (− 15.161, 16.315)	1.000	9.000 (4.034, − 13.966)	0.000*
	Study	3.630 (1.944, 5.315	0.000*	− 1.704 (− 8.026, 4.619)	1.000	− 1.852 (− 9.083, 5.379)	1.000	3.333 (0.270, 6.397)	0.270
Week 6 vs. 6 months	Control	6.115 (4.292, 7.939	0.000*	− 4.385 (−13.127, 4.358)	1.000	0.808 (− 15.995, 17.611)	1.000	12.577 (6.984, − 18.170)	0.000*
	Study	4.667 (2.328, 7.005	0.000*	− 4.037 (− 12.225, 4.181)	1.000	− 6.741 (− 16.323, 2.841)	0.600	5.000 (0.485, − 9.515	0.019*
3 months vs. 6 months	Control	1.385 (− 0.192, − 2.961)	0.158	− 6.000 (− 17.214, 5.214)	1.000	0.231 (− 10.464, 10.925)	1.000	3.577 (1.131, − 6.023)	0.001*
	Study	1.037 (− 0.119, 2.193	0.134	− 2.333 (− 6.872, 2.205)	1.000	− 4.889 (− 11.106, 1.328)	0.309	1.667 (− 1.282, − 4.615	0.847

. Analysis of variance for the outcomes dysgeusia and xerostomia, comparing the results of the same group at different times.
* When the *p*-value was statistically significant. MD = mean difference; CI = confidence interval; GST I = no stimulated salivary global test; GST lI = stimulated salivary global test.

Oral candidiasis

A total of 40 patients (75.4 %; 40 % of the CG and 60 % of the SG) developed OC at some point during follow-up. Among them, 34 (85 %, 32.5 % of the CG and 52.5 % of the SG) developed it only during treatment, 3 (7.5 %, 5 % of the CG and 2.5 % of the SG) only during follow-up, and 3 (7.5 %, 2.5 % of the CG and 5 % of the SG) in both periods. A statistically significant difference between the groups was only observed in the first week of treatment (p = 0.001), when 10 (37 %) of the patients in the SG developed candida infection, while none in the CG did. The frequency of OC in both groups throughout all periods is shown in Table 4 and Fig. 3c.

Trismus

Mouth opening did not change significantly throughout the follow-up period in both groups (Fig. 3d and Table 6).

Table 6
Mean of SGT I, SGT II, xerostomia, and trismus assessment, in the baseline period and in 3 weeks of treatment, and the follow-up period.

	Toxicities	SGT I		SGT II		Xerostomia Scale		Trismus	
Time	**Measures**	**Mean ± SD**	***p*-value***	**Mean ± SD**	***p*-value***	**Mean ± SD**	***p*-value***	**Mean ± SD**	***p*-value***
	Group								
Baseline	Control	41.77 ± 23.62	0.282	53.42 ± 26.08	0.179	19.73 ± 6.44	0.089	48.65 ± 7.66	0.012*
	Study	44.59 ± 17.22		57.70 ± 21.38		23.26 ± 7.47		42.41 ± 10.71	
Week 1	Control	32.15 ± 21.85	0.008*	44.65 ± 20.74	0.032*	27.04 ± 7.59	0.393[T]	46.85 ± 7.46	0.190
	Study	41.89 ± 17.17		52.93 ± 19.03		28.93 ± 8.33		43.74 ± 10.13	
Week 3	Control	29.96 ± 21.35	0.015*	42.73 ± 27.07	0.113	33.62 ± 9.69	0.922[T]	44.77 ± 7.16	0.735
	Study	35.56 ± 13.25		44.30 ± 15.53		33.89 ± 10.57		43.67 ± 10.00	
Week 6	Control	24.23 ± 17.19	0.001*	41.58 ± 29.61	0.015*	37.27 ± 10.13	0.493	43.12 ± 8.32	0.748
	Study	35.74 ± 12.72		45.07 ± 14.91		35.89 ± 10.12		42.67 ± 11.83	
15 days Follow-up	Control	22.15 ± 13.34	0.000*	41.08 ± 28.19	0.054	35.31 ± 9.90	0.957	44.08 ± 8.89	0.979
	Study	34.30 ± 12.41		44.00 ± 16.70		35.22 ± 11.02		43.81 ± 10.94	
2 months Follow-up	Control	26.12 ± 14.05	0.000*	39.85 ± 23.27	0.017*	32.69 ± 9.78	0.722[T]	46.00 ± 6.50	0.544
	Study	38.89 ± 13.20		46.81 ± 15.68		33.63 ± 9.26		44.19 ± 10.75	
3 months Follow-up	Control	22.62 ± 11.19	0.000*	41.00 ± 26.22	0.011*	28.27 ± 9.24	0.096[T]	46.65 ± 6.09	0.218
	Study	37.44 ± 13.18		46.93 ± 14.00		32.56 ± 9.15		44.33 ± 9.12	
6 months Follow-up	Control	28.62 ± 18.25	0.001*	40.77 ± 20.25	0.001*	24.69 ± 8.81	0.010*[T]	46.62 ± 7.32	0.950
	Study	39.78 ± 14.21		51.81 ± 14.78		30.89 ± 7.98		46.19 ± 8.31	

Note: *Student's t*-test were reported when it was possible [(T)], but most group comparisons were made using the *Mann-Whitney* test.
* When the *p*-value was statistically significant. SD = standard deviation; SGT I = no stimulated salivary global test; SGT II = stimulated salivary global test.

Discussion

Results such as ours have motivated organisations such as MASCC (Mucositis Study Group of the Multinational Association of Supportive Care in Cancer), ESMO (European Society for Medical Oncology) and WALT (Word Association Laser Therapy) to incorporate recommendations for PBM. These recommendations go beyond prophylaxis and OM treatment to encompass other oral toxicities associated with antineoplastic treatment [7,14,18,19]. The first MASCC guideline recommending prophylactic PBM for OM specifically referred to patients undergoing RT for H&N without concomitant CT, where a frequency of approximately 90 % development of clinically significant OM was reported [11,14]. However, their latest update also included the recommendation of PBM prophylactic for patients receiving CRT, with 100 % of patients potentially experiencing clinically significant OM [11,14]. Our observations corroborate these data, as all patients in the study experienced some degree of OM; however, none of the patients in either group reached OM grade IV, according to the World Health Organization (WHO) classification.

PBM is credited with mitigating the pathophysiological cellular damage effects by promoting the cellular oxidation control and inflammatory modulation [14,33–35]. This fact probably explains the differences observed between the groups, with the PBM-receiving group showing a delay in the onset of OM. Only 15.8 % of the patients who developed OM in the first week of treatment belonged to the PBM group, and until the second and third weeks, no patient in this group presented grade 3 OM. This situation is similar to that described by Oton-Leite et al. [36] and Antunes et al. [37]. Finally, at two-month follow-up, no patient in the PBM group presented OM, while 23.1 % of the control group still had grade 1 OM. These findings are consistent with previous studies that have demonstrated the effectiveness of PBM in accelerating healing and reducing the duration of OM. [18,36,37]. In addition to PBM application, variables such as tumour location and stage, as well as individual factors such as age (young) and gender (female), have been suggested as risk predictors for the development and severity of OM [38].What was not confirmed in our cohort, as demonstrated by logistic regression analysis, is that only the intervention group exerted an influence on OM.

Continuing with the identification of physiological effects promoted by PBM, we find its ability to regulate cellular oxidative stress [39,40],

Table 7
The OR for to determine if the group was a predictor of the decrease in saliva produced was calculated. The statistical analysis for the univariate OR was performed using binary logistic regression analysis. For reference values, we used "normal salivation" for the GST I and "normal glandular function" for the GST II.

Time	GST I			GST II		
	Covariate			Covariate		
		Univariate OR (95 % CI)	*p* value		Univariate OR (95 % CI)	*p* value
Baseline	normal salivation Vs. extreme hyposalivation	2.111 (0.433 – 10.284)	0.355	normal glandular function Vs. glandular hypofunction	3.500 (1.066 – 11.495)	0.039*
	normal salivation Vs. mild hyposalivation	1.520 (0.388—5.960)	0.548			
Week 1	normal salivation Vs. extreme hyposalivation	6.906 (1.702 – 28.026)	0.007*	normal glandular function Vs. glandular hypofunction	4.614 (1.437—14.817)	0.010*
	normal salivation Vs. mild hyposalivation	19.125 (2.919—125.319)	0.002*			
Week 3	normal salivation Vs. extreme hyposalivation	19.125 (2.919—125.319)	0.002*	normal glandular function Vs. glandular hypofunction	1.961 (0.590—6.517)	0.272
	normal salivation Vs. mild hyposalivation	3.333 (0.588—18.891)	0.174			
Week 6	normal salivation Vs. extreme hyposalivation	7.200 (1.787—29.011)	0.005*	normal glandular function Vs. glandular hypofunction	1.404 (0.410—4.805)	0.589
	normal salivation Vs. mild hyposalivation	0.800 (0.150—4.258)	0.794			
15 days Follow-up	normal salivation Vs. extreme hyposalivation	4.644 (1.239—17.413)	0.023*	normal glandular function Vs. glandular hypofunction	1.167 (0.333—4.089)	0. 810
	normal salivation Vs. mild hyposalivation	0.629 (0.095—4.177)	0.631			
2 months Follow-up	normal salivation Vs. extreme hyposalivation	0.267 (0.052—1.361)	0.112	normal glandular function Vs. glandular hypofunction	3.360 (0.976—11.563)	0.055
	normal salivation Vs. mild hyposalivation	0.991 (0.934—1.052)	0.769			
3 months Follow-up	normal salivation Vs. extreme hyposalivation	21.333 (4.416 – 103.066)	< 0.001*	normal glandular function Vs. glandular hypofunction	1.961 (0.590 – 6.517)	0.272
	normal salivation Vs. mild hyposalivation	2.667 (0.417—17.046)	0.300			
6 months Follow-up	normal salivation Vs. extreme hyposalivation	19.600 (4.025—95.449)	< 0.001*	normal glandular function Vs. glandular hypofunction	6.875 (1.858—25.432)	0.004*
	normal salivation Vs. mild hyposalivation	1.167 (0.160 – 8.526)	0.879			

* When the *p*-value was statistically significant. OR = Odds Ratio; CI = confidence interval; GST I = no stimulated salivary global test; GST II = stimulated salivary global test.

and consequently, the regulation of proinflammatory (IL-6, IL-1β, and TNF-α) and anti-inflammatory cytokines levels (IL-10 and TGF-β), and growth factors (NF-κB) present in the mucosa and saliva of patients undergoing antineoplastic regimens [36,41,42]. Considerable progress has been made in understanding the OM pathogenesis [34], and it is known that the increased level of all these cytokines during and at the end of antineoplastic treatment is one of the main factors inducing cellular damage [34,41]. Other studies have investigated the action of these cytokines on salivary gland cells and also on the development of OC [36].

Oton-Leite et al. [36] reported that, after 35 sessions of PBM, a significant reduction in IL-6 and FGF levels was observed, along with a slightly lower concentration of TGF-β, IL-10, IL-1β, and TNF-α in the salivary expression of patients in the PBM group compared to the control group at most time points evaluated. They suggested that lower levels of cytokines result in less damage to cellular tissues due to a less exacerbated inflammatory response [39]. Analysing these data together with the results of GST I and GST II obtained in our study, contrary to what was reported by Louzeiro et al. [43] and in agreement with the findings previously described by Gonneli et al. [44] and Mozaffari et al. [45], salivary alterations showed a delayed onset and were less pronounced in the PBM group, resulting in a significant difference between the groups. Based on the above results, we propose the hypothesis that PBM not only exerts a protective factor on oral mucosal cells, but also on the regenerative capacity of acinar cells. This prevents tissue fibrosis and consequently reduces glandular function, thereby maintaining normal saliva production and preventing another common and concerning oral complication, hyposalivation [18,43,46]. Our hypothesis is supported by Bomfin et al. [47], who reported an increase in apoptosis of acinar-ductal epithelial cells when higher levels of the aforementioned cytokines are present.

Saliva plays an important role in maintaining multiple functions in the oral cavity [48,42]. Therefore, a hyposalivation condition can lead to changes in the composition of the oral microflora as well as negatively impacting xerostomia and worsening the quality of life of patients [43,46]. The oral microflora changes including increased susceptibility to infections by Candida spp., which in turn also induce the production of proinflammatory cytokines (IL-1β and IL-6). Clemente et al. [49], also

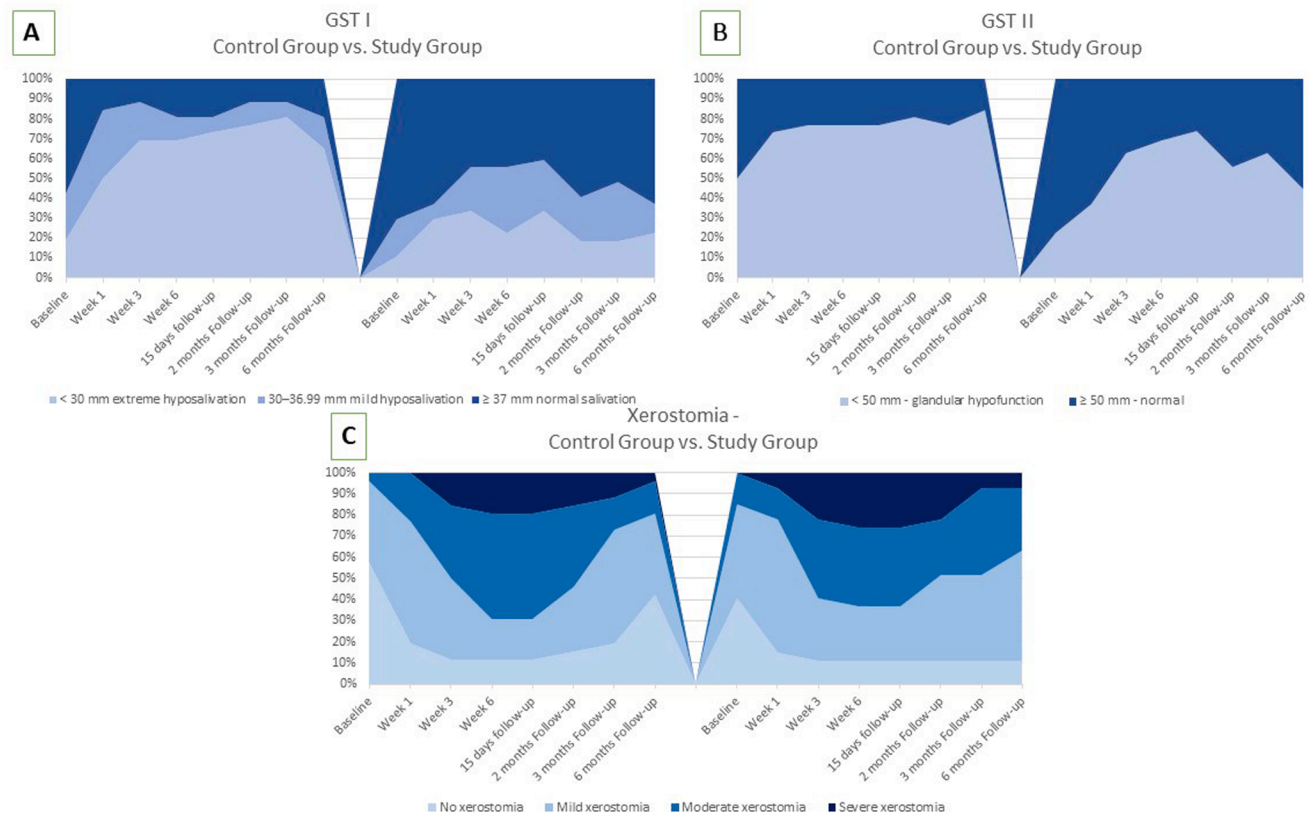

Fig. 4. Graphic of the variation of assessment of outcomes over the time of treatment and follow-up. **4a.** GST I **4b.** GST II **4c.** Xerostomia.

reported that PBM is able to control the levels of such cytokines. Through *in vitro* culture, they observed that infrared laser PBM significantly inhibited the ability of fungal cells to stimulate the production of inflammatory cytokines. In studies in which Candida albicans was irradiated *in vitro* with infrared laser, it was observed that PBM stimulated the proliferation of hyphae instead of destroying them [50,51]. The facts reported above, combined with the fact that only the control group received treatment with chlorhexidine 0.12 % mouthwash [52], could explain why in our study the frequency of OC, although not statistically significant, was higher in the PBM group. However, this group showed a significantly lower difference in the risk and severity of OM compared to the control group, contrary to the correlation between OC and OM reported by some authors [53,54]. Although all cited studies [49–51] used PBM with infrared laser, in our study red lasers were used for applications in the oral cavity.

In addition, changes in the amount of saliva may be accompanied by the feeling of a dry mouth, xerostomia [18,44,45]. This situation is of concern, as it is often associated with a decrease in quality of life [18,43]. In our study, during the baseline period, more than 80 % of patients in both groups had a low score on XI, indicating a “no xerostomia” situation. However, as treatment progressed, both groups showed an escalation in the XI score. Mozaffari et al. [45] related less xerostomia on the PBM group in weeks four to six. In the present study, although the escalation was lower in the PBM group, no significant difference was observed between the groups, which is in agreement with the results presented by Louzeiro et al. [43]. This contrasts with the results of Carvalho e Silva et al. [55], who observed lower scores in the PBM group, resulting in a significant difference in xerostomia symptoms between the group that received PBM and the group that did not.

Regarding the anti-inflammatory and analgesic effects attributed to PBM [39,56] in our patients, the pain experienced was similar in both groups during most weeks. A significant difference in favour of the PBM group was only observed at week 5 and at the 15-day follow-up, when less severe pain was reported compared to the CG. Our findings are not in agreement with those of other authors [57,58], who report that PBM was effective in reducing pain in all assessments. Similarly, in our study, there was no difference were in the need for analgesic use between the groups. This result, as reported by de Pauli et al. in their recent review [57], differs from most of the available literature, as of the 6 included studies comparing PBM and control groups, only 2 reported no statistically significant differences between the groups. These results may be due to the fact that our study assessed pain resulting from antineoplastic treatment overall, rather than focusing specifically on pain resulting from OM, as measured in most published studies [57].

In terms of dysgeusia, it was observed that 100 % of patients in both groups experienced some taste alteration perception during the treatment, corroborating the data presented by Epstein et al. [59]. Interestingly, it was observed that similar to OM, the group receiving PBM had a slower progression and developed a lower degree of dysgeusia over the course of treatment compared to the control group. Multiple factors causing dysgeusia may be present simultaneously in an oncological patient. In addition to antineoplastic therapy, factors such as salivary gland hypofunction and OC infection can also contribute [18,59]. Our theory is that PBM, as in OM, promotes proliferation and repair of the neuroepithelial cells that constitute the taste buds. It has been reported that taste change during the RT often coincides with mucosal damage, suggesting damage to the epithelial components of taste receptors [59,60]. There are currently no clinical studies using PBM to prevent dysgeusia in patients undergoing antineoplastic treatment [18]. There is only two case series in which PBM was used to mitigate OM in patients with H&N, and an improvement in the degree of dysgeusia was observed [59].

Finally, regarding trismus, although the mean mouth opening measurements of the control group were consistently lower than those of the PBM group, no significant differences were observed between the groups. The percentage of patients in this situation was within the range

reported by Watters et al. in their review, ranging (95 %IC = 10,8%-26,5%) at the start to a peak of 44.1 % at 6 months (95 %IC = 34,7%-51,8%) [31]. And, according to the same authors [31], trismus begins to increase immediately after treatment, and the percentage of patients experiencing it continues to increase over the following 6 months. Our results do not corroborate this observation because at the end of treatment, which in our study corresponds to week 6, it is when we observe the highest percentage of patients with trismus, and at the 6-month follow-up, the percentage observed returns to values similar to those of the baseline period. There are no clinical studies using PBM as prevention or treatment of trismus, so our results cannot be contrasted with existing data [18]. However, although fibrosis appears to be the primary factor in the development of trismus, there are other potential causal factors in patients with H&N [6,18]. In our study, PBM was applied to the oral mucosa, so it was expected that trismus resulting from factors other than epithelial fibrosis would not be prevented, although a systemic effect of PBM is suggested [61].

Our study had three primary strengths., First, we aimed to adhere to recommendations of a standardised protocol, reporting all criteria used to measure and analyse variables, thus allowing reproducibility and facilitating the comparison of our results with other studies following the same principles. Second, we sought to evaluate and include all acute side effects produced by antineoplastic therapy in H&N, which the literature suggests may benefit from or be mitigated by PBM. We tried to provide as many results as possible in text, tables, or graphs, and to conceptualise them in accordance with the literature available on the subject so far. Third, we also acknowledge some limitations. The antineoplastic treatment is carried out according to individual planning, so it has not been possible to control the dose and distribution of radiation (Gy). Also, there is a potential assessment bias, including the occasional use of mouthwashes and oral coatings. All patients were instructed not to use any products not prescribed by the medical team, but omission of the use of non-recommended products cannot be ruled out. Lastly, there was a relatively short follow-up period; effects were evaluated up to 6 months after treatment, therefore, long-term effects of PBM were not demonstrated, especially with regard to variables such as xerostomia, dysgeusia, hyposalivation and trismus, which according to the literature continue to develop years after the end of treatment [18,59].

Conclusions

The analysis of the results obtained in this study provides a detailed insight into how PBM influences the side effects of head and neck cancer treatment in the oral cavity. Although PBM apparently does not act to prevent the toxic effects of antineoplastic treatment, it can be concluded that, considering the parameters used and the follow-up time of this study, PBM proved its ability to delay the onset and decrease the severity of oral mucositis and hyposalivation; mitigate pain and dysgeusia at critical times (week 5 and 15 days follow-up, and week 6 and 15 days follow-up, respectively); however, it did not result in an overall improvement or worsening in relation to xerostomia, trismus, candidiasis and analgesic use.

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Author Contributions

GCVC; Conception and design of the study. Acquisition of data: data collected. Analysis and interpretation of the data collected. Drafting of article and/or critical revision. Final approval and guarantor of the manuscript. **IBPP;** Conception and design of the study. Acquisition of data: data collected. Final approval and guarantor of the manuscript. **RLL;** Conception and design of the study. Drafting of article and/or critical revision. Final approval and guarantor of the manuscript. **AGC;** Conception and design of the study. Drafting of article and/or critical revision. Final approval and guarantor of the manuscript. **ABC;** Drafting of article and/or critical revision. Final approval and guarantor of the manuscript. **AGG;** Conception and design of the study. Drafting of article and/or critical revision. Final approval and guarantor of the manuscript. **PGV;** Conception and design of the study. Drafting of article and/or critical revision. Final approval and guarantor of the manuscript. **MPSG;** Conception and design of the study. Acquisition of data: data collected. Analysis and interpretation of the data collected. Drafting of article and/or critical revision. Final approval and guarantor of the manuscript.

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CRediT authorship contribution statement

Gisela Cristina Vianna Camolesi: Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Irene Beatriz Prado-Pena:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Antonio Gómez-Caamaño:** Writing – review & editing, Supervision, Resources, Conceptualization. **Concepción Victoria-Fernández:** Writing – review & editing, Supervision, Methodology. **Andrés Blanco-Carrión:** Writing – review & editing, Conceptualization. **Abel García-García:** Writing – review & editing, Resources, Conceptualization. **Pilar Gándara-Vila:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Mario Pérez-Sayáns:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2025.107266.

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