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Efficacy of photobiomodulation therapy combined with mobile health education in patients with head and neck cancer suffering from chronic xerostomia after radiotherapy: protocol for a three-arm, randomised, placebo-controlled, double-blinded study

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ABSTRACT

Introduction The role of photobiomodulation (PBM) therapy for oral tissue damage induced by cancer treatment is currently unclear, and there is low-quality to moderate-quality evidence supporting the use of this approach for treating xerostomia and/or hyposalivation. Consequently, patients with head and neck cancer increasingly turn to basic oral hygiene to alleviate salivary gland dysfunction, and their adherence can be improved by mobile health (mHealth) education. The primary objective of this study will be to analyse the effects of different doses of PBM therapy (7.5 J/cm^2 vs 3 J/cm^2) plus mHealth education on quality of life (QoL), oral health, salivary secretion and salivary gland ultrasound assessment at postintervention and at the 6-month follow-up in patients with head and neck cancer after radiotherapy compared with those in control group.

Methods and analysis A prospective, three-arm, randomised, placebo-controlled, double-blinded study will be conducted among patients with head and neck cancer suffering from chronic xerostomia. A total of 20 patients per arm will be included and randomly assigned to receive 7.5 J/cm^2 of PBM, 3 J/cm^2 of PBM or placebo therapy. PBM therapy will be applied during 24 sessions at 22 points extra and intraorally two times per week for 3 months, combined with a mobile application (https://www.laxer.es). The assessments will be recorded at the beginning of the study, at postintervention and at the 6-month follow-up. The primary outcomes will be QoL, oral health, salivary secretion and salivary gland ultrasound. The pain pressure threshold, functional performance, mood and sleep quality will be secondary indicators.

Ethics and dissemination This study received ethics approval from the Andalusian Biomedical Research Ethics Portal (2402-N-21 CEIM/CEI Provincial de Granada) according to the Declaration of Helsinki for Biomedical Research. The results of this study will be presented at national and international conferences and published in peer-reviewed journals.

Trial registration number ClinicalTrials.gov NCT05106608.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ All the parameters of the intervention are described in detail for optimal reproducibility by healthcare professionals.
⇒ The sample size was calculated to yield a statistical power of 95% (α=0.05) to detect precise differences in the outcome, allowing a maximum attrition rate of 15%.
⇒ Some outcome measures will be measured objectively, which will allow the quantitative results to be differentiated from the patients' perceptions.
⇒ The intervention will be completely masked to all patients and assessors, but blinding physiotherapists to the dose of photobiomodulation therapy will not be possible.
⇒ A 6-month follow-up may not be sufficient to determine whether the results last over time.

INTRODUCTION

Oral tissue damage, which can be caused by radiotherapy (RT) combined with

chemotherapy and/or surgery, is one of the main side effects of treatment in patients with head and neck cancer (HNC).[1 2] Specifically, salivary glands lose their function, and patients may experience oral dryness or xerostomia, which is not always associated with objectively lower salivary secretion levels or hyposalivation.[3 4]

Xerostomia and/or hyposalivation have become important problems in patients' daily life because of significant health impairments in terms of feeding[5 6] and an increased risk of mouth infections.[7] Patients may also experience social and work-related limitations with respect to speaking skills, which often leads to emotional damage and may even result in trouble exercising and sleeping well, thereby negatively impacting their quality of life (QoL).[8] In fact, other studies have shown that xerostomia in patients with HNC extends far beyond poor oral health, and some of the most impactful aspects are pain[9 10] and functional limitations.[11] Furthermore, patients with hyposalivation also exhibited decreased QoL, with some of the most pronounced problems being insomnia and anxiety.[12] Therefore, all these outcome measures are linked to xerostomia and/or hyposalivation. This situation results in unmet needs related to oral health that should be addressed with new and effective strategies.

Although the pathophysiology of these oral side effects has not been fully elucidated, it could be considered a multifactorial disease.[13] The main reason is that salivary gland damage is strongly related to RT parameters (radiation dose, fraction size, irradiated tissue volume, fractionation scheme and type of ionising irradiation), but it is impossible to distinguish these RT-induced changes from those related to cancer disease, concomitant systemic diseases and other cancer treatments.[8] Therefore, a more comprehensive assessment of oral tissue damage and its impact on QoL should be carried out so that healthcare professionals may provide appropriate supportive care.

To date, the management of xerostomia has been supportive. Chronic xerostomia results in profound and potentially life-long side effect, reduces oral health-related QoL[8] and remains a significant burden for many patients.[14] However, the evidence on the benefits of pharmacological treatments, such as the procholinergic drug pilocarpine, which is used for the chemical stimulation of salivary secretions, is of low quality; this treatment has only minor effects and is accompanied by several unpleasant systemic adverse effects.[15] Furthermore, this approach has been associated with contraindications that limit its use.[16 17] Therefore, new methods have been gaining prominence as alternatives to pharmacological methods. Examples of these methods include physical stimulation such as acupuncture and transcutaneous electrical nerve stimulation or artificial saliva products and hyperbaric oxygen therapy, all of which have limited supporting evidence. Even mesenchymal stem cell and gene transfer therapies have been proposed, although they have not yet been sufficiently investigated.[15 18 19] Although the mechanics of photobiomodulation (PBM) are still not fully understood, the evidence suggests that this therapy can modulate the functional capacity of the glandular parenchyma, inducing salivary production.[20] The main advantage of this physical salivary stimulation method, together with the other methods mentioned above, is that it can reduce the incidence of or eliminate adverse effects compared with chemical stimulation methods.[21] The literature indicates that PBM has promising potential for the treatment of salivary gland dysfunction, although additional research is necessary.[22]

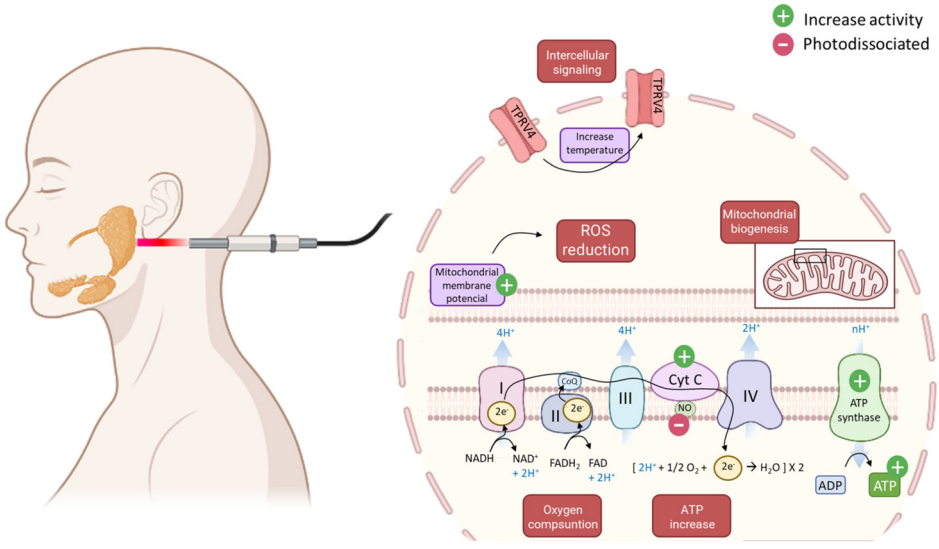

Figure 1 Photobiomodulation therapy. Created with Biorender.com under Academic License Terms (agreement number: RX265QWXOS). The acronyms are as follows: ADP, Adenosine diphosphate; ATP, Adenosine triphosphate; FAD, flavin adenine dinucleotide; $FADH_2$, Reduced form of flavin adenine dinucleotide; NAD^+, Nicotinamide adenine dinucleotide; NADH, Reduced form of nicotinamide adenine dinucleotide; ROS, Reactive oxygen species; TRPV4, transient receptor potential cation channel subfamily V member 4.

There has been a considerable increase in the application of PBM therapy (figure 1), previously termed low-level light or laser therapy,[23] for cancer treatment (in particular oral toxicity), although there is limited evidence in terms of its cost-effectiveness.[24 25] As part of a comprehensive update of the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology clinical practice guidelines[26] for the management of oral mucositis, in 2019, the panel recommended the use of PBM in patients receiving hematopoietic stem cell transplantation high-dose chemotherapy or treated with HNC RT (with or without chemotherapy). These recommendations should be improved and extended to other oral toxicities.

Therapies are classified according to either prevention (before/during RT) or therapeutic application (after RT). The prevention approach of xerostomia and/or hyposalivation has been prioritised,[27] although there is a line of research focused on after RT.[16 22 28 29] In this regard, Palma *et al*[30] used 808 nm PBM therapy (7.5 J/cm^2) and improved salivary hypofunction and pH, although the design was based on a single experimental arm. In a randomised pilot study, Saleh *et al*[31] used 830 nm PBM therapy (71 J/cm^2) and did not yield conclusive results for those parameters for xerostomia and hyposalivation. In the latter, the small size of the study sample, the use of non-blinded assessors and the long duration elapsed since the end of RT could be behind the inconclusive findings. A step forward in clinical trials could be to digitalise supportive care for patients with HNC to some extent.

Although the evidence is limited, basic self-care habits could achieve symptomatic relief in these patients.[32] Oral hygiene is extremely important for preventing the worsening of complications, although non-adherence rates are extremely high (81%).[33] Mobile health (mHealth), as a modality of digital healthcare, aims to improve patients' QoL not only by collecting symptoms (electronic patient-reported outcomes (ePROM)) or providing evidence-based supportive care guidelines but also mainly by monitoring their oral hygiene. In this sense, there is a clear disadvantage to being eligible for digital healthcare projects to the detriment of patients with HNC compared with other patients with cancer, such as colon or breast cancer.[34–37] There are numerous studies that discuss how health education can improve certain habits and routines and how this can be transmitted through mHealth. For these reasons, it seems necessary to study how mHealth could complement face-to-face professional support for patients with HNC facing xerostomia and/or hyposalivation.[38]

Based on all of the above, there appear to be two major gaps in the scientific evidence: the lack of consensus on the exact PBM parameters, one of the reasons that may explain why PBM therapy has not become mainstream[8] and the lack of mHealth tools backed by scientific evidence to accompany these patients during the oncological process. Designing both strategies could be a great advance for patients who will learn about oral hygiene and will become involved in their oral healthcare and for healthcare professionals such as physiotherapists, who will have a tool to monitor the patient's progress and will have evidence on which parameters of PBM are most effective.

Study objectives and hypothesis

The primary objective of this protocol, called the low-level Light therApy for XERostomia (LAXER) study, will be to analyse the effects of different doses of PBM therapy (7.5 J/cm^2 vs 3 J/cm^2) plus mHealth as a digital complement to oral hygiene to improve QoL, oral health, salivary secretion and salivary gland ultrasound assessment at postintervention and at a 6-month follow-up among patients with HNC after RT compared with placebo control patients. Second, the efficacy of the intervention on pain pressure threshold, functional performance, mood and sleep quality will also be assessed.

Although there are no significant adverse events (AEs) associated with PBM therapy in the literature[28] and because PBM is a patient friendly treatment modality,[16] data on the AEs of PBM therapy and patient satisfaction with this therapy will be collected on completion of this study.

We hypothesise that PBM therapy combined with mHealth may improve xerostomia and/or hyposalivation and consequently enhance QoL in patients with HNC after RT.

METHODS

Study design and setting

This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials statement[39] (table 1) and was registered on ClinicalTrials.gov (NCT05106608). The trial will be reported according to the Consolidated Standards of Reporting Trials statement.[40] A prospective, three-arm, randomised, placebo-controlled, double-blinded study will be conducted among patients with HNC suffering from chronic xerostomia after RT to analyse the efficacy of PBM therapy, and the study will be conducted at the facilities of the BIO277 (Cuidate) research group at the University of Granada. This study started on 13 July 2022 and is estimated to be completed by July 2025.

Patients and public involvement

Patients and/or the public were not involved in the design of this study and will not be included in the recruitment or conduct of the study. Patients will only be involved as research participants. Individual feedback on their research participation will be given, and all participants will be invited to a lecture on the overall results of the study.

Nevertheless, for the delivery of healthcare via mobile applications that contain videos with information about HNC and oral side effects, as well as recommendations,

Table 1 Schedule of enrolment, interventions and assessments of the study

	Enrolment	Allocation	Post allocation		
					Close-out
Timepoint	**–T0**	**0**	**T0**	**T1**	**T2**
Enrolment:					
Eligibility screen	X				
Informed consent		X			
Ethics committee approval and trial registration	X				
Allocation		X			
Interventions:					
Photobiomodulation-A (7.5 J/cm^2) plus mobile health education			X		
Photobiomodulation-B (3 J/cm^2) plus mobile health education			X		
Control photobiomodulation plus mobile health education			X		
Assessments:					
Sociodemographic and clinical characteristics			X		
Quality of life			X	X	X
Oral health			X	X	X
Salivary secretion			X	X	X
Salivary gland ultrasound assessment			X	X	X
Pain pressure threshold			X	X	X
Functional performance			X	X	X
Mood			X	X	X
Sleep quality			X	X	X
Safety and satisfaction with photobiomodulation therapy				X	

–T0, before beginning of the study; T0, beginning of the study; T1, post intervention; T2, 6-month follow-up post intervention.

a participatory approach was used during development, where patients and healthcare professionals participated in this process voluntarily.

Eligibility of criteria

Patients will be included in the study if they meet the following inclusion criteria: men or women aged 18 years or older and were diagnosed with HNC; chronic xerostomia; received RT in the parotid, submandibular and/or sublingual salivary glands; grade 3 oral dryness according to the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0; medical treatment completed and in complete remission; received medical clearance for participation in this study; at least 1 month passed since the end of RT to avoid the possible presence of oral mucositis and/or radiodermatitis, which limits adherence to treatment and maximum 36 months[30 31 41]; no history of drugs/devices/products (pilocarpine, cevimeline, amifostine, oral devices, humidifiers or herbs) to prevent or treat xerostomia prior to study inclusion or no change in their use (no change in type or dose) for 2 months prior to study inclusion; and able to access mobile applications or living with someone who has this ability.

The exclusion criteria will be as follows: patients with metastases; a score<60 on the Karnofsky Performance Status Scale; contraindications to receiving PBM therapy (eg, cardiac arrhythmias, pacemakers, photosensitivity, drugs with photosensitising action and pregnancy); other comorbidities such as diabetes and polypharmacy; and retraction of the declaration of consent.

Recruitment

Patients who meet the eligibility criteria will be recruited through the department of radiation oncology, Virgen de las Nieves University Hospital (Granada) and the department of medical surgical dermatology and venereology, San Cecilio University Hospital (Granada).

Procedure

The flow chart of the study is shown in figure 2. Assessments will take place at the beginning of the study (T0), postintervention (T1) and at the 6-month follow-up (T2) and will be performed by a physiotherapist with more than 5 years of clinical experience.

Randomisation

A randomisation plan will comprise a permuted block of random sizes to ensure that a roughly equal number of

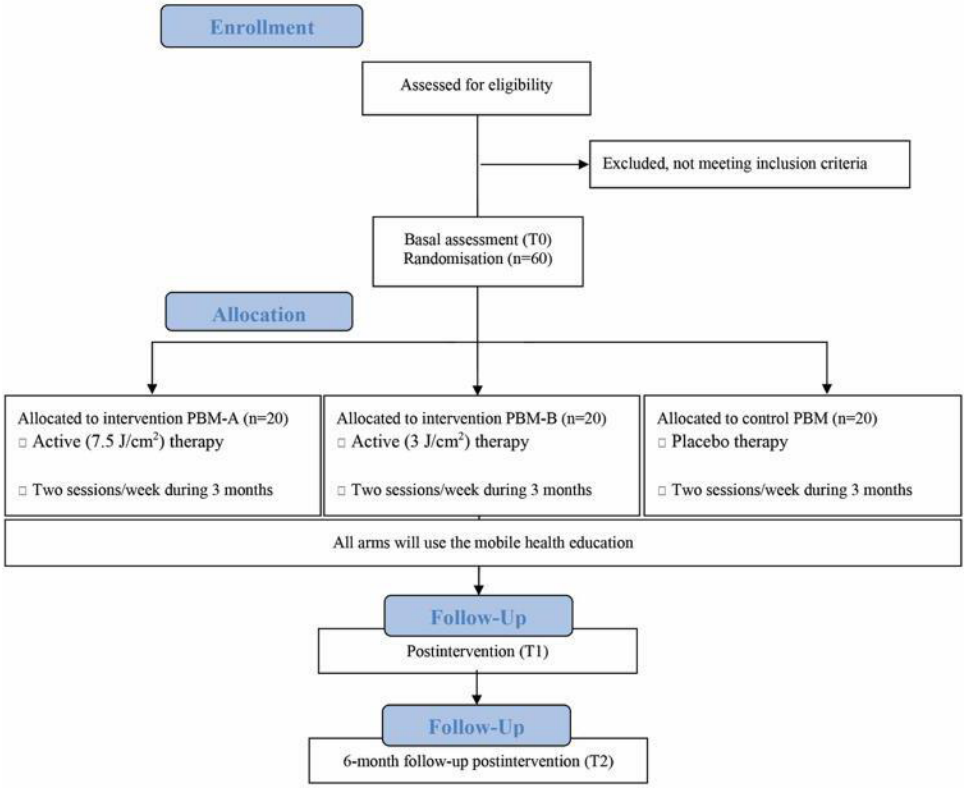

Figure 2 Flowchart of the study. PBM, photobiomodulation.

patients are assigned to each arm by the end of the study in a 1:1:1 allocation ratio (figure 2). A computer-based random number generator (www.randomizer.org) will be used to assign the patients to the three study arms.

Concealed allocation will be achieved by sequentially numbered, sealed, opaque envelopes. The mentioned plan will be created by an independent investigator and will remain password protected (known only by himself) for the duration of the study.

Blinding

All patients and the staff assessor will be masked to the random allocation. The effectiveness of the blinding will be assessed after the intervention assessment. The assessor will answer whether he thinks that the application of PBM was real or placebo or that he does not know. Afterwards, the assessor will ask the patient, 'Do you think that the application of PBM was real, placebo or did not know?'. Patient responses will be recorded and used to gauge the adequacy of patient and assessor blinding.

Intervention

The study is based on the Template for Intervention Description and Replication checklist.[42] PBM therapy will be applied by a trained physiotherapist with the laser model approved by the Food and Drug Administration. All intervention parameters are described following a previously published guide to ensure their reproducibility in the future[26] (table 2). The power output supplied by the laser device will be checked before and after intervention by means of a power metre supplied by the manufacturer (LaserPoint Srl, Vimodrone, Milan, Italy).

PBM therapy will be applied on 22 points described (figure 3). During the sessions, the physiotherapist and the patients will wear safety goggles with special lenses, and the laser device will be covered with disposable transparent plastic wrap in intraoral applications. The laser device and the skin of the patient's face will be disinfected with a 70% alcohol solution. Any AE with a direct relationship to study participation was the reason for discontinuing the allocated intervention.

The placebo control arm will undergo the same protocol used in the active arm and the same laser device to mimic real irradiation[43]; however, the laser will be turned off, and a recording with emission sounds will be used. This control arm has been used previously.[44 45]

Additionally, an mHealth tool will be available for the three arms at the onset of interventions, where all patients will have access to a multicomponent intervention. The application (https://www.laxer.es) collects behavioural change information by assessing QoL and oral health, providing a colour graphical summary from ePROM, unlocking content (oral hygiene) and the question and answer platform parallel to face-to-face PBM sessions. The content of these recommendations is based on the guidelines agreed on by the healthcare professionals involved and those published in the scientific literature.[46] The possibility of chatting with other patients or posing questions to professionals and reminders for PBM sessions

Table 2 Photobiomodulation therapy parameters using the model IIIb BTL-458-10IC, BTL-4000 Smart

Device setting-machine-determined	
Wavelength	830 nm
Spot size	0.021 cm² Multimode Sheaumann (M9-808-0500-03P)
Beam type	Convergent
Device setting-user-determined	
Power	53 mW
Irradiance	2.52 W/cm^2
Energy	Photobiomodulation-A 0.16 J/point 3.50 J/session Photobiomodulation-B 0.063 J/point 1.39 J/session
Time per point	Photobiomodulation-A 3 s/point Total: 66 s Photobiomodulation-B 1 s/point Total: 22 s
Energy density	Photobiomodulation-A 7.5 J/cm^2 Photobiomodulation-B 3 J/cm^2
Mode	Continuous
Intervention parameters	
Application	Intra- and extraoral
Timing	After radiotherapy
Frequency	Two sessions/week Total: 24 sessions 3 months (12 weeks)
Number of irradiated points per gland/anatomical point	Six extraoral points/parotid gland Three extraoral points/submandibular gland Two intraoral points/sublingual gland Total: 22 points/session The probe will be applied perpendicularly to, in slight contact with the skin and using disposable transparent plastic wrap in intraoral applications.

would be other services provided in the mobile application. All patients will receive an informative talk at the beginning of the study on how the application works. To motivate patients and increase adherence to treatment, the content of the application will be made available progressively throughout PBM therapy.

Outcomes

Primary outcomes

Quality of life

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) V.3.0. The EORTC QLQ-C30[47] comprises 30 items on 5 functional scales, 3 symptom scales, 6 single items and a global health scale measured by a 4-point Likert scale with a total score ranging from 0 to 100. Higher scores on the functional and global health scales indicate better functioning or QoL, respectively, but higher scores on the symptom scales or single items indicate a high level of symptoms. This is a validated and reliable questionnaire widely used in the oncology population (Cronbach's alpha>0.70).[48] In addition, the specific head and neck module (EORTC QLQ-H&N35)[49] will be used; this module comprises 35 items on 7 multi-item scales and 11 single items scored from 0 to 100. Higher scores indicate more symptoms. This tool has also been shown to be reliable (Cronbach's alpha>0.70).[50]

Oral health

The severity of xerostomia was assessed using the Spanish version of the Xerostomia Inventory, a reliable questionnaire (Cronbach's alpha 0.87–0.89) that consists of 11 items (score range 1–5) with a total score ranging from 11 to 55 points to rate the severity of chronic xerostomia. A higher score indicates more severe xerostomia.[51] Dysphagia will be measured using the Eating Assessment Tool-10, a validated and reliable questionnaire (Cronbach's alpha 0.96)[52] that consists of 10 items related to swallowing difficulties (score range 0–4, 0=no problem, 4=severe problem), with a total score of 3 or higher indicating dysphagia. For the assessment of perceived xerostomia, a numeric visual analogue scale will be used, with a grade ranging from 0 (no symptoms) to 10 (the worst possible symptoms).[53] The degree of mouth opening will be determined by the range of motion using a sliding calliper, which will measure the maximal interincisal distance in millimetres. Additionally, a total of 10 examples of clinical physical findings where each one represents a feature of dryness in the mouth will be administered through the Clinical Oral Dryness Score (CODS), a scale with good reproducibility for assessing dry mouth. A score of 2 or more indicates significant oral dryness.[54] The reproducibility of the CODS with respect to the intraclass correlation coefficient (ICC) varied from 0.89 to 0.96.[55] Along these lines, regional oral dryness will also be assessed with the Regional Oral Dryness Inventory. This questionnaire quantifies the severity of dryness at nine different locations in the oral cavity and is represented by nine illustrations. Patients will indicate the severity of perceived oral dryness using a 5-point Likert scale (1=none, 5=severe).[56]

Salivary secretion

The unstimulated and stimulated salivary flow rate will be calculated (mL/min). First, an unstimulated amount

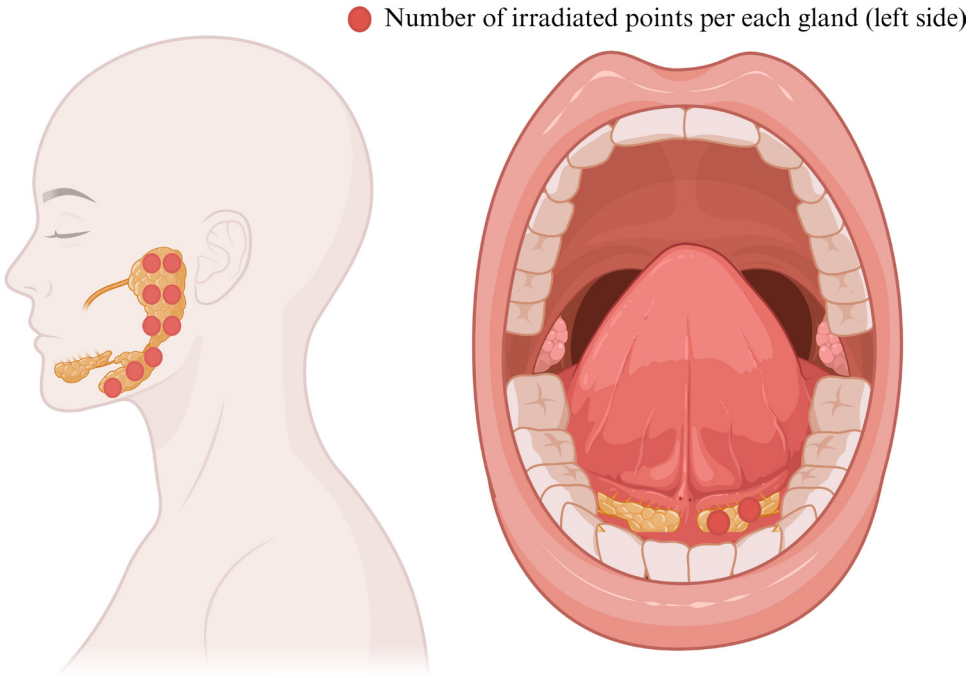

Figure 3 Location of irradiated points. Parotid, submandibular and sublingual salivary glands. Created with Biorender.com under Academic License Terms (agreement number: YA265QWOJW).

of saliva will be obtained by patients being seated with their head slightly inclined forward and will be asked to expel for 5 min in sterile and graduated tube.[57] To obtain the stimulated saliva, patients will stay in the same position and will chew a standard piece of paraffin for 5 min. The volume of each sample will also be calculated (in microlitres). All salivary samples will be collected in the early morning, and patients will be asked not to eat, drink (except water) or chew gum at least 1 hour before. Samples from unstimulated saliva will be used to analyse salivary biomarkers, such as proteins (eg, antibodies), calcium concentration and pH,[53] using commercial kits.

Salivary gland ultrasound assessment

The morphology of the parotid and submandibular glands will be assessed using two-dimensional echography (Samsung HM70A echograph) to quantify changes in size in three dimensions.[58] The ultrasound parameters will be adjusted according to the glandular ultrasound image of each patient and maintained throughout the follow-up.

Secondary outcomes

Pain pressure threshold

An electronic algometer (SENSEBox System, Somedic AB, Sösdala, Sweden) will be used to assess pain at seven body sites bilaterally: the C5-C6 joint, upper trapezius, elevator scapulae, masseter, temporalis, sternoclavicular joint and tibialis anterior distal point. The mean of the three measurements will be considered. This test has been shown to be reliable (ICC=0.91).[59]

Functional performance

Functional capacity will be assessed using the 6 min walk test. The maximum walked distance (metres) that patients are able to walk in a 30 m linear corridor will be quantified. A longer distance indicates better functional capacity. This test has been shown to exhibit moderate reliability (ICC=0.74).[60] Mobility/fall risk will also be assessed using the timed up and go test, in which patients sit back in a chair and walk toward a cone located 3 m away as quickly as possible. The time (in seconds) needed will be registered two times, with a shorter time indicating better mobility. This test has been shown to exhibit acceptable reliability (ICC=0.99).[61] On the one hand, perceived fitness status will be assessed using the International Fitness Scale, which refers to overall fitness, cardiorespiratory fitness, muscular strength, speed/agility and flexibility dimensions, using a 5-point Likert scale (1=very poor, 2=poor, 3=average, 4=good, 5=very good) (Cronbach's alpha=0.80).[62] On the other hand, physical activity level will be registered using the International Physical Activity Questionnaire—Short Form, a self-reported validated questionnaire for patients with cancer that records the activities of the previous 7 days according to intensity level. This is a validated tool in patients with cancer.[63]

Mood

The Spanish version of the Scale for Mood Assessment will also be used and comprises four subscales with good reliability (sadness–depression, anxiety, anger–hostility and happiness); the items range from 0 to 10 (0=nothing, 10=much). All the categories have shown good reliability (Cronbach's alpha=0.88–0.93).[64]

Sleep quality

Sleep quality will be measured using the Pittsburgh Sleep Quality Index, a validated questionnaire that includes 19 self-related questions ranging from 0 to 3. The total score ranges from 0 to 21, and a lower score indicates better quality of sleep (Cronbach's alpha 0.77–0.81).[65]

Other outcomes

Safety will be assessed by the occurrence of any AEs[66] using CTCAE V.5.0,[67] whereas satisfaction will be registered by a questionnaire previously used in other clinical settings at the end of the intervention.[68 69]

Power and sample size considerations

The power calculations and sample size will be determined for the primary outcome, the EORTC QLQ-H&N35 specific module,[49] through one component, oral dryness (xerostomia). Assuming that the PBM therapy arms will increase QoL in terms of oral dryness with an effect size of d=0.45 (based on a previous study)[70] compared with the control arm, with a power of 95% and an alpha level of α=0.05, with three arms, 17 patients will be necessary per arm. 60 patients in total (20 per arm for three arms) will be recruited to allow for a maximum loss to follow-up of 15% (G*Power V.3.1.9.2 for Windows) (online supplemental file 1).

For the estimation of the annual number of eligible patients, it must be emphasised that specific statistics on HNC in Granada (Spain) are not available. Therefore, the potential success in terms of patient eligibility has been extrapolated from previous studies (both prospective and cross-sectional) that involved patients with HNC and were conducted by the research team. Notably, two of these studies indicated a high participation response rate, surpassing the required sample size.[71 72] This fact, in conjunction with (1) inclusive eligibility criteria and (2) the observation that approximately 70% of irradiated patients with HNC suffer xerostomia and/or hyposalivation, increasing to 85% at 2 years after RT,[3 18 73] suggests an adequate annual number of eligible patients (estimation of the prevalence in men/women in Spain 2020: 71 927 and 23 122, respectively).[74] Regarding recruitment rates, past studies have demonstrated rates between 73% and 76%,[9 71 75] which indicates that a similar rate might be anticipated for the current trial.

Establishing an exact mortality rate is challenging owing to the absence of local reference data. Nonetheless, patients eligible for this trial were those who completed medical treatment and were in complete remission; these patients were categorised as disease-free survivors with HNC. Furthermore, given that the time span from the end of RT to the study varies from 1 to 36 months and considering a 5-year relative survival rate of 68% for these patients,[76] it is anticipated that the majority of patients will be alive during the study period, excluding deaths due to non-cancer-related causes.

Statistical analysis

Descriptive statistics will be used to summarise the sociodemographic and clinical metrics. Baseline characteristics will be compared between arms using independent sample (unpaired) t-tests and χ^2 tests (or their counterparts), and the efficacy of the intervention (difference between arms over time) will be determined using effect size expressed as Cohen's d, with calculated 95% CIs. If the data met a normal distribution, the efficacy analysis will be conducted according to the intention-to-treat principle and following an analysis of covariance with corresponding post hoc analysis with Bonferroni adjustment for multiple comparisons. The analysis will be adjusted for the effects of the following covariates: type of RT, RT dose, time since the end of RT, glandular dissection, age, cancer stage and xerostomia drug/device/product. To reduce adherence bias, a minimum of 75% attendance (≥18 sessions) will be required for a patient's data to be included in the analyses. All analyses will be performed using IBM SPSS Statistic V.26.

Data statement

Study data will be available on reasonable request. The complete individual participant data available to other researchers have been described in detail elsewhere (Clinicaltrials.gov).

ETHICS AND DISSEMINATION

This study obtained ethics approval from the Andalusian Biomedical Research Ethics Portal (2402-N-21 CEIM/CEI Provincial de Granada) and was carried out in accordance with Law 14/2007 on Biomedical Research[77] and the current version (2013) of the guidelines of the World Medical Association Declaration of Helsinki.[78] This study has been registered with Clinicaltrials.gov (NCT05106608). All patients will receive verbal and written information about the study and will sign an informed consent form (online supplemental file 2) before participating. At all times, patients will be able to withdraw or decline their participation.

No publication related to this protocol has been published or submitted to any other journal.

The results of this study will be presented at national and international conferences and published in peer-reviewed journals, as well as on social media, to facilitate the translation of science to lay audiences. The authorship of the publications emerging from the study will be decided based on the guidelines of the International Committee of Medical Journal Editors (ICMJE). Moreover, any required protocol modifications will be performed on the Clinicaltrials.gov website.

TRIAL STATUS

The trial is currently recruiting and is expected to be completed (including follow-up assessment) by July 2025.

DISCUSSION

This is an on-topic study protocol because it involves two doses of PBM therapy with parameters that meet international recommendations. Furthermore, this protocol prioritises methodological quality. A combination of face-to-face interventions that effectively increase QoL, plus mHealth education about oral hygiene, could result in reductions in patient costs and workload in healthcare systems. Jiang *et al*[79] have recently been proposed as a future research line to test adherence to oral hygiene instructions using an mHealth tool. Considering the results shown in cancer and non-cancer populations,[16] it is strongly believed that the LAXER study could represent the first integral management (face-to-face intervention plus education through mHealth) for patients with HNC once they overcome cancer treatment and could support them in minimising the impact of long-term side effects on their daily lives.[80]

The findings of this study clarify the importance of using PBM therapy in patients with HNC for therapeutic application because the literature lacks studies on the impact of PBM in patients with xerostomia and/or hyposalivation after RT.[22 41] Although physiotherapists provide valuable interventions across the whole spectrum of cancer care,[81] the proposed interventions will be performed during survivorship (after cancer treatment), where either available options have certain limitations (eg, pharmacological treatment)[82] or because of the small number of studies carried out to date, with contradictory results likely related to the PBM doses that were used[41] force to carry out new investigations into the role of PBM in the treatment of chronic xerostomia after RT.

This study is still subject to several limitations. First, physiotherapists involved in PBM therapy will not be blinded. Second, despite using a challenging follow-up (6 months), future studies should be designed to test whether longer periods are of greater benefit. Finally, it is important to highlight that the equivalence between onsite and digital methods (PROM vs ePROM) has already been widely demonstrated,[83] as has the equivalence between cancer patients,[84] and the ePROM will have identical and adapted content to the PROM version in terms of format and design via the Moodle platform. Therefore, this possible limitation of assessing by means of ePROM should be resolved. Moreover, the research group participating in this study has extensive experience in generating telehealth systems, which guarantees, in part, the successful implementation of this new mobile system.[35–37]

This protocol will analyse whether PBM therapy is better than a placebo and which dose (7.5 J/cm^2 vs 3 J/cm^2) is more effective. The expected benefits of this study include an improvement in clinical practice toward innovative ways of providing oral healthcare to patients with HNC after RT; moreover, the current evidence about the use of PBM for cancer therapy-associated salivary gland dysfunction is limited, and effective and long-lasting interventions are lacking. Furthermore, xerostomia is a symptom that can also affect non-cancer populations (those with polypharmacy, autoimmune diseases or hypertension; patients on hemodialysis; or those suffering from diabetes)[16]; thus, there are many potential patients who could benefit from its use, improving the profitability of the integral management described in this protocol.

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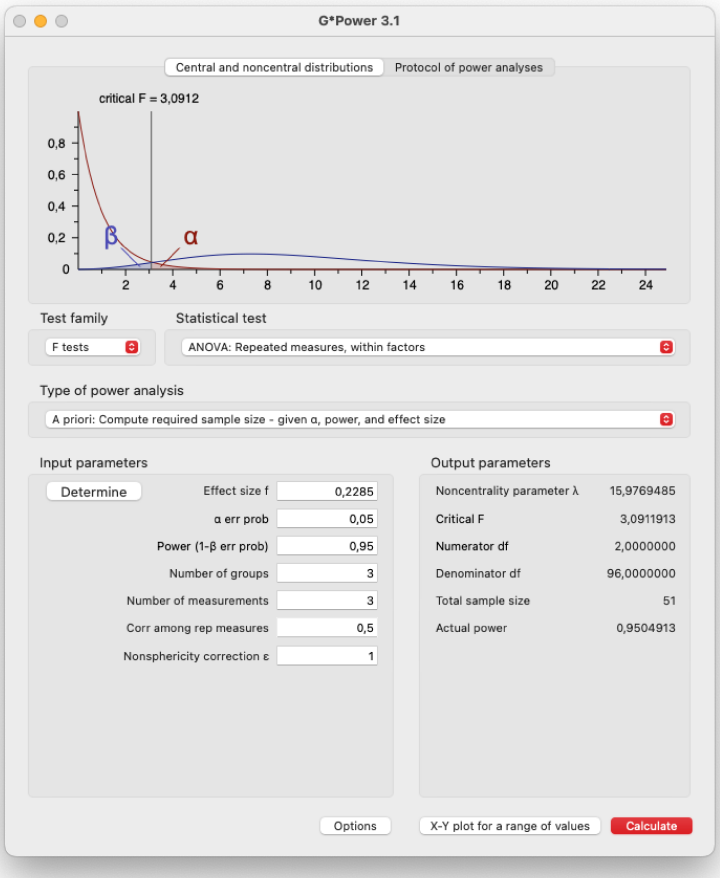

The power calculations and sample size will be determined for the primary outcome, the EORTC QLQ-H&N35 specific module, through one component, oral dryness (xerostomia). Assuming that the PBM therapy arms will increase QoL in terms of oral dryness with an effect size of d=0.45 (based on a previous study) compared to the control arm, with a power of 95% and an alpha level of α=0.05, with three arms, 17 patients will be necessary per arm. Sixty patients in total (20 per arm for three arms) will be recruited to allow for a maximum loss to follow-up of 15% (G*Power 3.1.9.2 for Windows) (online **supplemental file 1**).

CONSENTIMIENTO DEL PACIENTE

Este documento tiene como finalidad dejar constancia de que usted ha otorgado su consentimiento para su inclusión en el estudio denominado **"EFICACIA DE LA TERAPIA DE FOTOBIOMODULACIÓN COMBINADA CON UN SISTEMA DE M-HEALTH EN PACIENTES CON CÁNCER DE CABEZA Y CUELLO QUE SUFREN XEROSTOMÍA CRÓNICA DESPUÉS DE LA RADIOTERAPIA: ESTUDIO DOBLE CIEGO, ALEATORIZADO Y CONTROLADO CON PLACEBO"** y por tanto nos autoriza a intervenir en los términos acordados. Antes de firmar este documento, usted debe haber sido informado de forma verbal y por escrito sobre dicho estudio.

CONSENTIMIENTO

Manifiesto que estoy conforme con mi inclusión en el estudio propuesto, y que he recibido y comprendido satisfactoriamente toda la información, tanto de la hoja informativa, como de las preguntas que he creído convenientes realizar por mi parte, y que mi participación es totalmente voluntaria. Autorizo además el uso de mis datos para futuros estudios, siendo de obligado cumplimiento para ello que éstos se traten de manera totalmente anónima.

Así mismo, se me ha informado sobre mi derecho a solicitar más información complementaria, a la confidencialidad de los datos obtenidos, y a retirar mi consentimiento en el momento en que lo considere oportuno, sin obligación de justificar mi voluntad y sin que de ello se derive ninguna consecuencia adversa para mi persona. También manifiesto que he leído y comprendido toda la información sobre el estudio propuesto y dejado constancia de haber recibido la suficiente información sobre el estudio, y por tanto acepto mi inclusión.

Si requiere información adicional se puede poner en contacto con nuestro personal en el teléfono: 958 24 87 69 o a través de los siguientes correos electrónicos: noeliagaliano@ugr.es, aris.tovar@gmail.com, unidadcuidate@ugr.es

Datos del paciente:

D…… Firma……...

He sido informado por:

D…… Fecha……...

Yo, el abajo firmante, he explicado todos los detalles importantes de este estudio.

Firma del investigador……. Fecha: …….

CONSENTIMIENTO INFORMADO PARA LA TOMA DE MUESTRAS BIOLÓGICAS

En qué consiste:

Se le tomará una muestra biológica de su organismo. Las muestras biológicas más solicitadas en la práctica clínica son: sangre, orina, heces y esputo, aunque pueden recogerse otras.

Para qué sirve:

El estudio (bioquímico, citológico, microbiológico, etc.) de las muestras biológicas puede aportar información muy útil para un tratamiento más adecuado. Tan importante como su obtención es el manejo de la muestra, por lo que existen normas estrictas para la correcta recogida, manipulación, transporte y conservación de la muestra, así como para su adecuado procesamiento en laboratorio.

Riesgos y molestias:

La toma de muestras apenas presenta riesgos. Para garantizar la seguridad del paciente, se efectuará por personal sanitario capacitado y bajo condiciones de seguridad y de asepsia rigurosa.

En el caso de la toma de muestra salival no presenta riesgos. En algunos pacientes, por sus características individuales, puede producirse un ligero sangrado resultante de la encía sin suponer ningún riesgo para su salud.

Puede presentar una mínima incomodidad y sensación de sequedad bucal como consecuencia de la carencia de saliva que finalizará normalmente una vez finalizada la recogida de la muestra.

Responsabilidad del paciente:

Comparta con el personal del estudio de investigación la información sobre su estado de salud y cualquier sensación no habitual que experimente (especialmente sobre enfermedades que puedan transmitirse en contacto o manipulación de muestras biológicas). Usted es responsable de revelar completamente esta información antes de la recogida de saliva.

Preguntas:

Antes de firmar este formulario, le animamos a formular cualquier duda sobre los procedimientos utilizados. Si tiene dudas o preguntas, por favor pídanos otras explicaciones.

Declaro que he sido informado de los riesgos del procedimiento, que he leído este formulario y comprendido los procedimientos de la prueba y que sé que, en cualquier momento, puedo revocar mi consentimiento.

Estoy satisfecho con la información recibida, he podido formular toda clase de preguntas que he creído conveniente y me han aclarado todas las dudas planteadas.

En consecuencia, doy mi consentimiento para la recogida de muestras biológicas.

Datos del paciente:

D…… Firma……...

He sido informado por:

D…… Fecha……...

Yo, el abajo firmante, he explicado todos los detalles importantes de este estudio.

Firma del investigador……. Fecha: …….

DERECHO DE RETIRADA

Como participante en el estudio podré retirar mi consentimiento en el momento en el que lo considere oportuno, sin obligación de justificar mi voluntad y sin que de ello se derive ninguna consecuencia adversa para mi persona.

Confirmo que he sido informado/a sobre las características del estudio de manera adecuada:

SI NO

Entiendo que soy libre y puedo abandonar el estudio en cualquier momento sin perjuicio de que mis derechos se vean dañados:

SI NO

Datos del paciente:

D…… Firma……

He sido informado por:

D……Fecha ……

Yo, el abajo firmante, he explicado todos los detalles importantes de este estudio.

Firma del investigador……. Fecha: …….