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Photobiomodulation therapy to prevent oral mucositis and functional impairment in adult patients with haematological cancer undergoing haematopoietic stem cell transplantation: randomised trial protocol

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ABSTRACT

Introduction Oral mucositis is a highly prevalent condition in individuals treated for haematological neoplasms, primarily during haematopoietic stem cell transplantation (HSCT). The condition is known to delay recovery processes, increasing the risk of infection, the number of interventions and the length of hospital stays. The proposed Photobiomodulation Therapy for Oral Mucositis and Functional Impairment Transplantation Trial aims to assess the effectiveness and acceptability of using photobiomodulation in the oral cavity to prevent oral mucositis and functional impairment in adult patients undergoing HSCT.

Methods and analysis This is an assessor-blinded and statistician-blinded, parallel-group randomised controlled clinical trial (photobiomodulation vs control group). Participants and setting: 30 patients, aged 18–65 years, with haematological neoplasms undergoing HSCT at the Clínica Dávila Oncology and Bone Marrow Transplant Unit. Primary outcome measures: oral mucositis will be assessed daily using the WHO grading scale, beginning on the day of transplant through day 20 post-transplant. Researchers will assess functional capacity using a 2 min step test, handgrip strength with the Jamar digital dynamometer, lower limb strength using a 30' sit-to-stand test and quality of life with the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation Questionnaire. Acceptability will be assessed by logging treatment adherence and using a Visual Analogue Scale. Assessments will occur at two time points (1): on admission to the transplant unit, before starting the conditioning regimen and (2) on the day of discharge. Intervention: three times per week photobiomodulation therapy using a diode laser device will begin the first day of conditioning and continue through day 3 post-transplant.

Ethics and dissemination The Clínica Dávila and Universidad del Desarrollo Clinical Research Ethics Committees approved this study in accordance with the Helsinki Declaration. Patients' informed consent will be required. The dissemination strategy includes publication in scientific journals as well as presentations in the media and at conferences.

Trial registration number NCT06260111.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ One strength of this trial is its assessment of physical function outcomes (handgrip strength, functional capacity, physical fitness) in patients undergoing stem cell transplantation who received (or did not receive) photobiomodulation preventive treatment.
⇒ Another strength is the measurement of the acceptability of photobiomodulation therapy during haematopoietic stem cell transplantation.
⇒ One limitation of the study is the short follow-up, which is up to the day of hospital discharge when patients no longer exhibit oral mucositis.
⇒ Another limitation is the impossibility of blinding patients and therapists considering the unavailability of a sham equipment.

INTRODUCTION

Haematological neoplasms are a heterogeneous group of malignant diseases that affect the blood, lymph nodes and bone marrow.[1] Haematological diseases such as leukaemia, Hodgkin's and non-Hodgkin's lymphoma and multiple myeloma were respectively responsible for 3.1%, 2.6%, 0.2% and 1.2% of all cancer deaths worldwide in 2020. That same year, an estimated 475 000 new cases of

leukaemia and 544 000 cases of non-Hodgkin's lymphoma were reported.[2]

Despite advances in cancer treatments, the diversity of therapeutic options and the increase in overall survival rates, the side effects of cytotoxic treatments have increased morbidity and disability-adjusted life years in cancer survivors.[3] Among the most frequently experienced are cancer-related fatigue, nausea, weight loss and oral mucositis (OM),[4] which all impact the cancer survivors.[3]

OM is a frequent side effect of chemotherapy and radiation therapy. Patients who receive high doses of chemotherapy with or without total body irradiation before a haematopoietic stem cell transplant (HSCT) are at high risk for developing OM.[5] OM occurs in approximately 60%–85% of transplant patients,[6] with the greatest severity between days 6 and 9 post-HSCT.[7]

The functional impact of mucositis is mainly due to malnutrition. During HSCT, pronounced weight loss (>7% of body weight) has been associated with a higher risk of fungal infection complications (48% vs 23%, OR 3.37; 95% CI 1.11 to 10.19) compared with a modest weight loss (<2% of body weight).[8] Furthermore, the parameters of body weight and body mass index (BMI) have been described as predictive of the results of allogeneic transplants. Compared with individuals with a normal BMI, those with a low BMI (<18.5) have a higher risk of general mortality, relapse and daily mortality at day+100 post-HSCT.[9]

More severe degrees of mucositis have been associated with an increased risk of infection and fever in patients receiving autologous HSCT. In those undergoing allogeneic HSCT, more severe degrees are associated with more days of parenteral nutrition, days of injectable narcotics, hospital expenses and mortality at day+100 post-HSCT.[10] In patients undergoing allogeneic HSCT with myeloablative or reduced-intensity conditioning, the incidence of any degree of OM has been 73.2% and 86.5%.[11]

There are a variety of therapeutic options for managing mucositis. Preventive strategies include anti-inflammatory drugs, herbs, growth factors, cryotherapy, laser and light therapy.[12] Oral cryotherapy during a pretransplant chemotherapy infusion focuses on decreasing the incidence and severity of OM,[13] parenteral nutrition use and hospital stay length.[14] However, its effectiveness as a prophylactic tool during chemotherapy is controversial due to the lack of evidence.

In 2014, a panel from the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) published clinical guidelines for OM management, recommending the use of photobiomodulation (PBM), also known as low-level laser therapy, for prevention in patients undergoing HSCT conditioned with high-dose chemotherapy, with or without total body irradiation, and in patients undergoing head and neck radiation therapy without conventional chemotherapy.[15] In 2020, MASCC/ISOO updated the guidelines, again recommending PBM and outlining evidence-based, clinically effective application protocols for mucositis prevention.[16]

Bezinelli *et al* described the cost-effectiveness of introducing an oral care protocol that includes PBM in the management of patients undergoing HSCT.[17] According to the authors, this therapy helps reduce morbidity and, consequently, minimises transplant-associated hospitalisation costs. Moreover, prior to the introduction of PBM, patients were more likely to have severe mucositis, to receive parenteral nutrition for longer periods, to have greater need for opioids and opioid days and to experience more pain in the oral cavity. Hospitalisation costs were up to 30% higher.[17] The use of PBM for the prevention of mucositis has been described as safe. A retrospective study evaluating short-term and long-term safety in 693 patients undergoing HSCT found no evidence of immediate or late adverse effects or the development of secondary malignant neoplasms in the oral cavity.[18] Nevertheless, a recent systematic review of PBM for mucositis in patients undergoing HSCT identifies the need for more randomised studies with greater methodological rigour, mainly in parameter definition.[19]

PBM is known to reduce weight loss and prevent BMI reduction in patients with head and neck cancer.[20] While functional impairments related to handgrip strength, functional capacity and physical fitness are common after HSCT,[21–23] PBM's role in preventing such functional impairments remains unidentified. In addition, PBM effectiveness in improving overall and oral-health-related quality of life has not been previously observed in patients undergoing HSCT.[24] Thus, further experimental studies are required to evaluate the effectiveness of PBM for preventing OM in patients with haematological cancer receiving HSCT, its impact on other functional outcomes.

No studies have been found exploring the acceptability of PBM from the user's perspective. The PBM for OM and Functional Impairment Transplantation Trial proposes an innovative approach by considering the patient's opinion on this therapeutic tool. This is relevant data for implementing this type of intervention in health facilities. The main objective of this study is to assess the effectiveness and acceptability of PBM in the oral cavity to prevent OM and functional impairment in adult patients undergoing HSCT. Our hypothesis states: (1) PBM prevents severe OM, resulting in better clinical and functional outcomes (pain, hospital stays, opioid doses, handgrip strength, functional capacity, physical fitness, nutritional status and quality of life); (2) researchers expect the intervention to show moderate/high acceptability among patients.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Trial design

The study design involves a randomised controlled trial with parallel groups (experimental vs control). It is assessor-blinded and statistician-blinded with a 1:1 allocation ratio (figure 1). Patients and therapists will not be blinded considering the unavailability of a sham

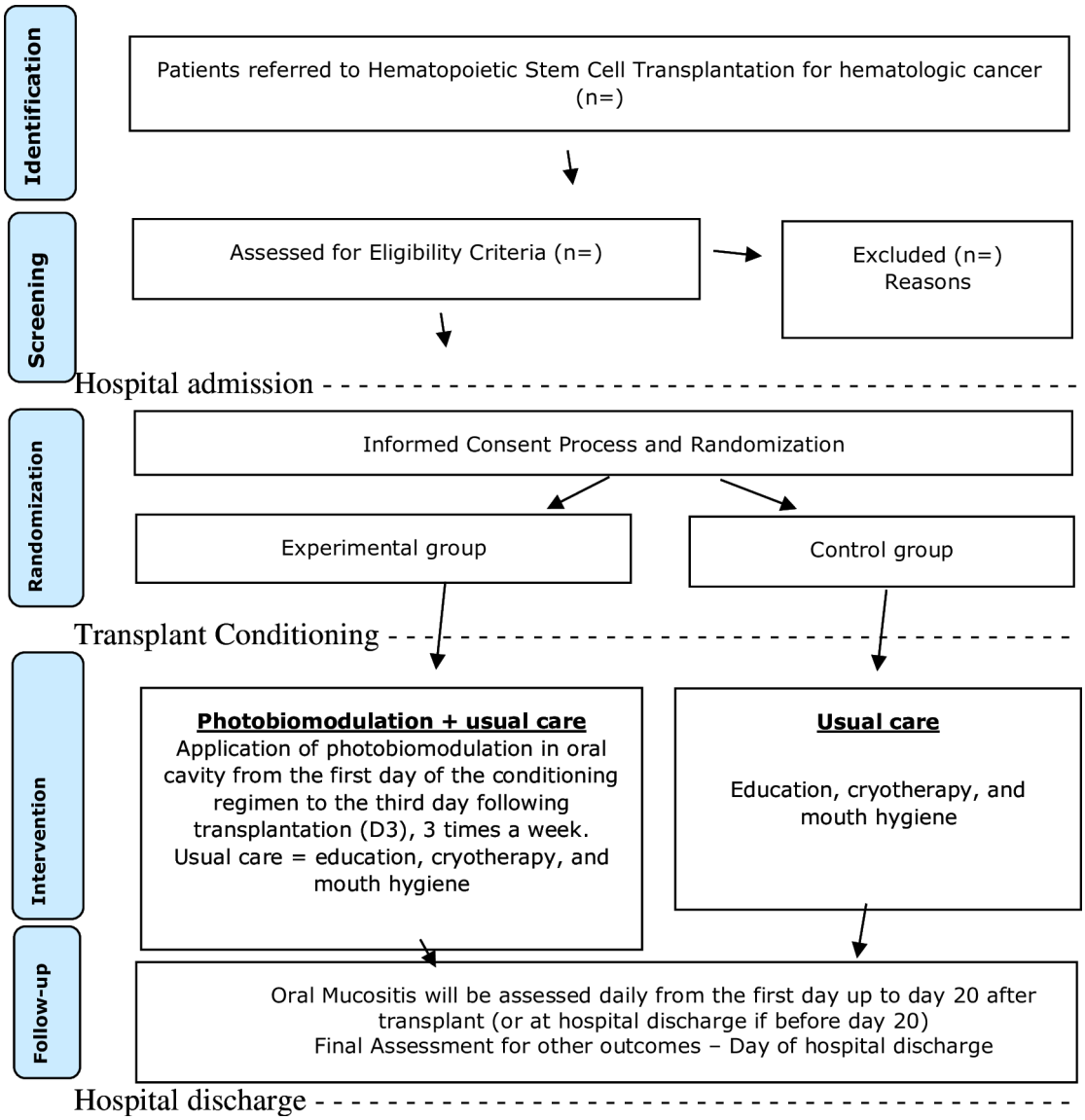

Figure 1 Flow diagram of the study design.

equipment. Data collection began in June 2024 and is expected to end in March 2025.

Patients will be randomly assigned to the experimental group (PBM+usual care) or the control group (usual care). Both groups will receive the same guidance on oral hygiene (usual care) per institutional prophylaxis protocol.

The report on this protocol meets the requirements of the Standard Protocol Items: Recommendations for Interventional Trials.[25]

Study setting

Potential participants will be recruited at Clínica Dávila Recoleta in Santiago, Chile. Evaluations and interventions will occur during the participant's hospitalisation at the institution.

Participants and eligibility criteria

Adults, aged 18–65 years, with haematological neoplasms whom the Clínica Dávila Transplant Committee has selected to receive an HSCT at the institution under the National Protocols for Hematopoietic Transplant[26] will be invited to participate 1 week before their HSCT admission date. Participants must have a sufficient understanding of Spanish.

Exclusion criteria will be any observed cognitive deficit or failure to meet the clinical stability or disease progression criteria and National HSCT Programme requirements. Participants with any type of oral *Candida* infection prior to HSCT will also be excluded. In accordance with institutional HSCT guidelines, a dentist will perform an oral screening for *Candida* prior to admission for the HSCT. The haematologist and the institution's HSCT coordinating nurse will recruit participants by referring any patients who meet the eligibility criteria of the study.

A researcher, the physical therapist or the nurse, will obtain the patient's informed consent (online supplemental file 1). The process will begin with a comprehensive explanation of the study, assessments, procedures,

risks and benefits. Patients will be given the time necessary to ask questions and express concerns regarding the study. They will receive a printed copy of the informed consent form so they can read it carefully and, if they so desire, take it home for further analysis. The consent form will be signed on admission to the transplant unit.

The sample size was calculated using the G*Power program given the proportion of patients with grade 0 or 1 mucositis (WHO OM grading scale) in the PBM group (82.4%) and in the control group (38.9%).[27] The alpha value was 0.05, with a power of 0.80. Thus, the required sample size is 30 patients (15 in each group), which is feasible considering that Clínica Dávila carried out 38 haematopoietic transplants in 2022.

INTERVENTIONS

Explanation for the choice of comparators

The study compared the group receiving PBM plus usual care with a control group receiving only usual care to determine whether including PBM to prevent mucositis impacts functional parameters by optimising nutritional intake, encouraging oral intake and reducing pain, given its potential analgesic effect on the oral mucosa. For ethical reasons, the control group will also receive a preventive measure, like cryotherapy, that is part of the usual care for reducing mucositis symptoms.

Intervention description

A haematology unit physical therapist with postgraduate oncological rehabilitation studies and PBM experience will receive training on using PBM per the study protocol before performing the intervention in the patient's private room at the Clínica Dávila. The intervention will not delay the infusion times for conditioning chemotherapy or other pretransplant interventions nor interfere with oncological clinical decision-making processes. It will be carried out during the day at a time agreed on with the patient to ensure a safe, comfortable experience.

The intervention being tested, PBM or low-level laser therapy, will be carried out three times per week, beginning on the first day of the conditioning and continuing through day 3 post-transplant (D3). The duration of the conditioning regimen depends on the type of transplant, usually varying from 2 (autologous) to 7 days (allogeneic); meaning that patients will receive approximately three to six PBM sessions. MASCC/ISOO recommends using PBM daily between the first day of conditioning and day+2 post-HSCT. The decision to deliver PBM three times per week aimed to reduce costs and number of sessions, which could make the intervention more feasible to implement in clinical practice. The parameters (dose and frequency) were calculated to keep them within the recommended therapeutic window.

The intervention protocol is based on previous studies demonstrating the effectiveness of PBM for OM.[16 24 28] PBM will be applied in 7–10 min sessions. An InGaAlP diode laser (DMC Laser therapy EC) with the following parameters will be used: wavelengths of 660 nm (red) and 808 nm (infrared), 100 mW power output and 2 J of energy measured at the 0.001 cm^2 tip of the fibre optic. The laser will be applied at 20 points in the oral region, with an exposure time of 20 s per point, using 2 J of energy per point (figure 2). The total energy applied per day will be 40 J. One finger width will be used to separate applications and avoid overlap. Since the laser will be applied with tissue contact, a protective covering will be used on the equipment per institutional hygiene standards.

Both groups (control and intervention) will receive the usual care for mucositis during the transplant. Per institutional protocol, this includes education, cryotherapy and oral hygiene. The unit's HSCT coordinating nurse will educate patients and encourage daily mouth washing. The trial allows all participants to receive the usual care in terms of institutional oral prophylaxis and rinsing measures. However, no medications, ointments or non-pharmacological interventions that interfere with OM are allowed during the trial.

The oral hygiene protocol involves rinsing with sodium bicarbonate and double-distilled water every 6 hours and after each meal, starting the day before the chemotherapy conditioning period. Even if the patient has no desire to eat, an oral rinse is performed to neutralise the pH of the oral mucosa. Oral hygiene aims to prevent opportunistic infections at the start of the gastrointestinal tract. In case of pain, lidocaine may be added to the double-distilled water. When OM, detected per WHO criteria, causes intense pain, Gelclair may be added to mouthwash before meals to reduce pain and optimise oral intake. When cytarabine is administered for conditioning with chemotherapy before HSCT, one drop of Oftason in each eye is used to protect the mucous membrane. Oftason administration is initiated on the evening before the start of cytarabine and lasts until the day before HSCT (D1).

Cryotherapy involves administering ice chips and/or pineapple sorbet 20 min before melphalan infusion, for 45 min during and 20 min after infusion.

The institutional care protocol for hospitalised post-transplant patients includes physical therapy at least two times per day. Physical therapy involves aerobic exercise with a pedal exerciser, resistance training using 1 kg dumbbells and/or elastic resistance bands, stretching, breathing and diaphragmatic re-education and a respiratory exerciser.

The PBM intervention will be discontinued if the patient's condition worsens due to the transplant, at the patient's request or if any adverse effects occur. The intervention will be performed in a pleasant environment, ensuring the patient's comfort and convenience as a strategy for improving adherence.

Patient and public involvement

Patients were not involved in designing the study. Researchers talked to some patients about the study protocol and listened to their opinions. The six patients

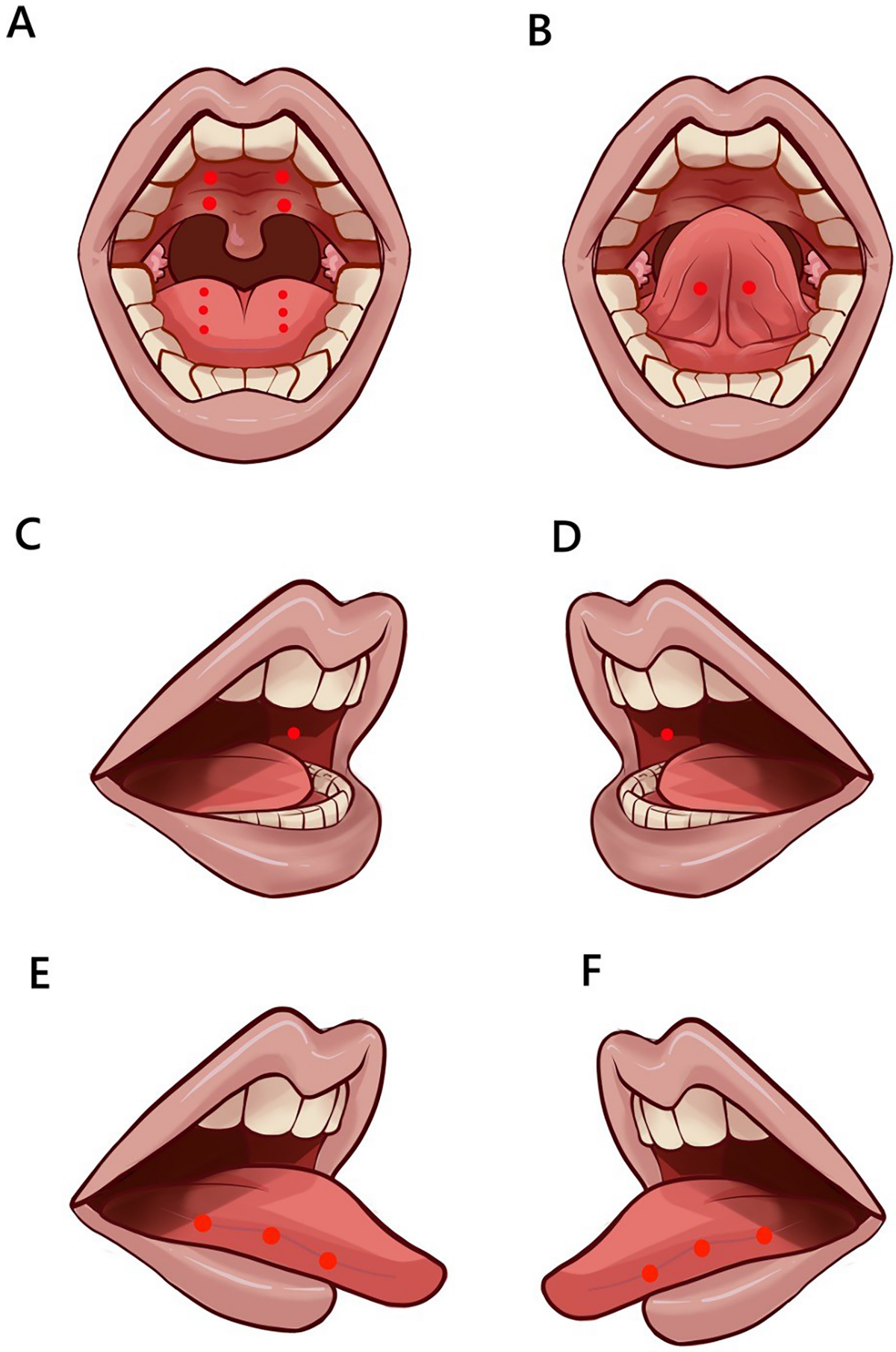

Figure 2 Location of the points of low-level laser therapy application.

consulted remarked that it was a great proposal that could potentially help patients undergoing HSCT.

Outcome measures

Assessments will occur on the day of admission to the unit (T1) and the day of hospital discharge (T2). Meanwhile, participants will be assessed for OM daily, beginning the day after the transplant (D1) until the day of hospital discharge, which may occur about a month post-transplant (D20) (table 1).

Main outcome: mucositis

OM, specifically the maximum grade of OM developed after stem cell transplant, is the primary outcome measure in this study. OM grades will be recorded daily, beginning the day after the stem cell transplant until day 20 post-transplant. In both study groups, a clinical assessment of severity will be conducted using the WHO scale, where oral lesions are classified as grade 0=none; grade 1=oral soreness/erythema; grade 2=erythema, ulcers, able to tolerate solid diet; grade 3=ulcers, liquid diet only and grade 4=oral alimentation impossible.[29] The intensity of OM-associated pain will be logged using a visual analogue scale from 0 to 10 (0=no pain, 10=the worst possible pain).

Secondary outcomes: physical function (handgrip strength, functional capacity, physical fitness), nutritional status, quality of life, clinical outcomes and acceptability

Several functional tests will assess physical function/fitness to determine the patient's functional and physical condition.

Handgrip strength: a hydraulic hand dynamometer (Jamar Digital Plus) will measure handgrip and upper limb strength. This low-cost device is easy to use, and the test results have demonstrated prognostic value in all-cause mortality in patients with cancer.[30] The test subject sits in a chair with their back against the backrest, shoulders close to the trunk, without rotation, elbow flexed to 90 degrees, forearm and wrist in a neutral position and both feet on the floor. The evaluated arm does not rest on any surface, and the dynamometer is positioned vertically. The subject exerts maximum isometric grip strength for 3 s, with a 1 min rest between the two attempts.[31] The higher value is recorded for subsequent analysis.

Functional capacity: this refers to an individual's exercise capacity as measured by endurance (maximum duration and/or workload achieved) during an exercise test. The performance measure is the 2 min step test (2MST), a functional test that assesses an individual's aerobic capacity. The test has been previously administered with older adults in a community setting[32] and used in the oncology population to determine correlation with the Eastern Cooperative Oncology Group Performance Status (ECOG PS), resulting in a moderate Spearman's correlation coefficient (r=−0.54).[33] The test subject stands next to a wall and lifts their knees to walk in place for 2 min. The step height, the midpoint between the participant's lateral femoral condyle and anterior superior iliac spine, is marked on the wall. The professional conducting the test counts and records the number of times the right knee reaches the marked target during the 2 min.[34]

Physical fitness: this is the ability to perform daily tasks and physical activities in a highly functional state, often as a result of physical conditioning. The 30' sit-to-stand test assesses the subject's ability to rise from a chair and sit back down, as well as lower-limb strength and functionality.[35] Initially developed for older adults (66–97 years),[36] it has been used in the oncology population. Researchers found a modest correlation between test values and ECOG PS (Spearman's correlation r=−0.491).[33] The test subjects cross their arms over their shoulders and stand from a standard chair (43 cm) to a bipedal position with legs fully extended as many times as possible within 30 s. The score is the number of times the participant rises completely from the chair during the allotted time.

Nutritional information: researchers will consult the patient's clinical file to obtain the mean daily calorie intake (kcal/day) after transplant and the number of days of parenteral nutrition support. They will calculate BMI using patient weight (kg) and height (cm), measure arm circumference at the midpoint between the olecranon and the acromion with a relaxed arm and the elbow flexed to 90 degrees and use a skinfold calliper to measure triceps skinfold thickness. In addition, researchers will evaluate the patient's nutritional status using an overall register of nutritional status according to the Global Leadership Initiative on Malnutritio Criteria.[37] This scale classifies participants into three categories: well-nourished, mildly/moderately malnourished or severely malnourished.

Quality of life: researchers will use the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation Questionnaire (FACT-BMT)[38] to assess quality of life. The questionnaire, available in Spanish, is a validated instrument widely used in the oncology population undergoing HSCT. It was obtained directly from the FACIT group with authorisation for use in this study. FACT-BMT has been previously compared with the EORTC QLQ-C30 questionnaire, revealing a sufficiently high correlation for dimensions related to overall quality of life in transplant patients.[39] Silva *et al*[24] used the questionnaire to determine the impact of PBM on OM and quality of life in patients undergoing HSCT.

The 50-item FACT-BMT questionnaire (fourth version) evaluates five dimensions as they apply to a patient's past 7 days: physical well-being, social/family well-being, emotional well-being, functional well-being and a bone marrow transplant subscale. The response format is a 5-point Likert scale: 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much. Some items have reverse scoring. A higher score indicates a better quality of life.[38]

Acceptability: researchers will use a visual analogue scale from 0 to 10 (0=no acceptability, 5=moderate acceptability and 10=optimal acceptability) to assess acceptability among patients in the intervention group. Adherence to the PBM sessions will also serve as an indicator of acceptability since the professional performing the intervention

Table 1 Schedule of enrolment, interventions and assessments

	Enrolment	Allocation	Postallocation	Follow-up and intervention				Close-out
Timepoint	$-t_1$	0	t_1	–D	D0	D3	Up to D20	t_2
			Baseline (at hospital admission)	Chemo(radio) therapy conditioning	Stem cell transplantation			D20/Discharge
Enrolment								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Interventions								
Photobiomodulation				◆———	———	———◆		
Control group								
Assessments								
Sociodemographic	X	X						
Clinical information			X					X
Oral mucositis						X	X	X
Physical function*			X					X
Nutritional status†			X					X
Quality of life			X					X
Length of hospital stay								X
Use of opioids								X
Acceptability				X	X	X		X

D0=day of haematopoietic stem cell transplantation; D3=third day after transplant; D20=day 20 after transplant or at hospital discharge.
*Handgrip strength, functional capacity, physical fitness.
†Subjective global assessment, number of days of parenteral nutrition, body mass index, mean of daily calorie intake, arm circumference, triceps skinfold.

will ask the patient whether they are willing to receive PBM and log the response on the daily record sheet.

Likewise, researchers will use electronic hospital records to determine the length of hospital stay (admission to discharge) and the number of days from transplant to engraftment.

They will also consult electronic medical and/or nursing records to determine the quantity of analgesic opioids administered to manage OM, tracking the number of times the patient requested and received analgesic medication to alleviate OM pain between the onset of OM and medical discharge.

For descriptive purposes, researchers will take the following sociodemographic and health information from hospital records: age (years), gender, type of cancer, cancer stage, type of treatment received prior to HSCT (eg, chemotherapy, radiotherapy or immunotherapy), conditioning regimen for HSCT and patient-declared comorbidities (eg, diabetes, hypertension, depression/anxiety, respiratory disease, smoking or alcohol consumption).

ASSIGNMENT OF INTERVENTIONS: ALLOCATION

Sequence generation

An independent individual will use randomising computer software to assign participants to groups. Sequence generation will be performed in blocks of 10.

Concealment mechanism

Sealed opaque envelopes will be used to conceal allocation.

An independent individual will generate the allocation sequence. After screening for eligibility, the enrolling researcher will use sealed and numbered envelopes to assign participants to the next available allocation. The therapist conducting the experimental group's treatments will assign participants to interventions.

DATA COLLECTION AND MANAGEMENT

Plans for assessment and collection of outcomes

The centre's HSCT coordinating nurse will evaluate OM according to WHO criteria. A physical therapist other than the one performing the intervention will assess secondary outcomes (physical tests) at the two time points. A nutritionist from the haematology unit will evaluate the nutritional aspects.

Plans to encourage participant retention and complete follow-up

Per institutional usual care, the physical therapy team will visit patients daily to promote physical activity and exercise. The transplant coordinator will also visit daily to assess the patient's condition and encourage participation in physical therapy. These visits will create connections with the patient and positively reinforce the study.

STATISTICAL METHODS

The data will be tabulated in Excel spreadsheets and analysed with the SPSS V.20 software. Frequency distribution, central tendency measurements (mean, median) and dispersion (SD, IQR) will be used for descriptive analysis. Researchers will use the Shapiro-Wilk test, symmetry and kurtosis analysis to test for data normality.

For intergroup comparisons of pre-intervention and post-intervention outcomes, mean/median differences and their CIs will be computed. Student's t-test for independent samples or its non-parametric equivalent, the Mann-Whitney U test, will also be used. Intragroup comparisons will use Student's t-test for pairing samples or its non-parametric equivalent, the Wilcoxon test. A subgroup analysis will be performed by type of transplant (ie, autologous or allogenic). A p value <0.05 will be adopted.

The analysis will be based on the intention-to-treat principle.

Protocol adherence could be affected for different reasons, for example, death, non-tolerance of treatment or side effects. In any case, the number of PBM sessions the patient receives will be recorded. The researchers propose an intention-to-treat analysis, where the average score from the corresponding group (intervention or control) would be used in place of any missing data, if necessary.

Ethics and dissemination plans

Ethical approvals: the Clínica Dávila and Universidad del Desarrollo Clinical Research Ethics Committees (2013-111) have approved this study.

Data management and confidentiality: the haematology and transplant unit team will protect the patients' personal information. Only the research team will handle assessment data, which they will store in a special physical folder at the institution. The Excel spreadsheets of the data will be anonymous and use numerical codes for each participant.

Unblinding will occur only if required by ethical and regulatory committees. In that case, significant protocol modifications will be communicated to the ethical committees, trial registration, sponsor and institution funding the research.

This clinical trial involves a widely studied therapy supported by scientific evidence and assessments commonly used with patients with haematological cancer undergoing HSCT. As such, the trial will not include an external data monitoring committee. However, an internal committee, comprising the lead researcher and the researchers assessing the primary outcomes, will monitor preliminary safety-related data and conduct ongoing preliminary data analyses for safety and efficacy. If any adverse events are reported, the committee will request analysis and recommendations from external dentists with expertise in PBM. The data monitoring committee is independent of the sponsor and the institution funding the research.

Adverse event reporting and harms: low-level laser therapy is below the threshold associated with adverse thermal effects or mechanical cellular damage.[40] Systematic reviews found that studies involving PBM reported no adverse effects.[41 42] Only one of the systematic reviews found a study reporting that 15% of patients experienced an immediate (non-painful) burning sensation after intra-oral 635 nm diode laser treatment.[43] As studies with long-term follow-up were not found, the MASCC recommended caution when using PBM in areas with known or possible tumours. The patient must be informed of the potential benefits and risks.[43]

The local Research Ethics Board will audit the study independently of the researchers and sponsor.

Patients will be asked if they present any adverse events, such as erythema, pain, burns, oedema or any other event correlated to the treatment. Tolerability will be assessed via patient self-reporting.

Dissemination: study results will be sent to indexed journals for review and distributed to study participants via email. Researchers will apply the International Committee of Medical Journal Editors authorship recommendations when publishing the results.

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Contributors TL-E, CS: conception or design of the protocol, protocol register, manuscript writing and editing and final approval of the version to be published. PA-C, DQ, PR, MP-E, LFdR, HL-V: design of the protocol, manuscript editing and final approval of the version to be published. CS is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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