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[Intervention Protocol]

Interventions for preventing oral mucositis in people receiving cancer treatment: photobiomodulation

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of photobiomodulation for the prevention of oral mucositis in people undergoing treatment for head and neck cancers, other solid cancers, and haematological cancers.

BACKGROUND

Description of the condition

Oral mucositis is a complication of cancer treatment with chemotherapy, radiotherapy, a combination of radiotherapy and chemotherapy, targeted therapies, or haematopoietic stem cell transplantation. Overall incidence rates for people receiving radiotherapy to the head and neck are typically around 90%, and 83.5% for people undergoing haematopoietic stem cell transplantation [1, 2]; rates may be higher when both chemotherapy and radiotherapy are used as treatment options for head and neck cancers [3]. However, incidences vary across all cancer types and may be underreported, particularly for cancers for which people are treated as outpatients, when severity of oral mucositis is less, or when people may wish to avoid disruption to optimal cancer treatment [4]. Children and adolescents may be more prone to developing oral mucositis than adults, although symptoms in this population group may resolve more quickly [5].

Oral mucositis is a manifestation of an inflammatory response within the oral mucosa (the mucous membrane lining the cavity), and can affect all parts of the mucosa. Ulceration is the most significant stage of the condition, as it leads to pain of varying severity. This can impact eating, swallowing, talking, medication adherence (particularly for medication taken orally), and oral hygiene [6, 7, 8]. In some cases, people with oral mucositis may need either a modified diet or parenteral nutritional support (i.e. nasogastric or intravenous feeding). They will also require additional oral care, increased medical appointments, and in some instances, hospitalisation [9, 10, 11]. Thus, the negative impact on the quality of life of people with cancer, when they are already suffering, is severe (8). Further problems can occur in people who are immunosuppressed and are experiencing a disruption of homeostasis or dysbiosis of specific oral bacteria, which can lead to bacteraemia and sepsis that require antibiotics and hospitalisation, and can cause death [4, 9, 12]. Oral mucositis can be a dose-limiting condition, disrupting a person's optimal cancer treatment plan [9, 12, 13, 14, 15].

It is an acute condition. When caused by chemotherapy, ulceration normally occurs five to 14 days after treatment and resolves within three weeks of treatment [2, 16]. Radiotherapy-induced oral mucositis takes longer to both develop and heal, with ulceration normally occurring around three weeks into a treatment cycle, and resolving within one to 14 weeks [2, 17].

The additional costs associated with oral mucositis are significant, with incremental cost estimates between USD 5000 to USD 30,000 for people receiving radiotherapy, and USD 3700 per cycle for people receiving chemotherapy [18]. Another study estimates the incremental costs for those receiving radiotherapy, chemotherapy, or radiotherapy with molecular targeted therapy as high as USD 33,560 per person [19]. For people receiving haematopoietic stem cell transplantation, these costs may reach USD 299,000 per person [19].

Description of the intervention and how it might work

Photobiomodulation therapy uses red or near-infrared light, lasers, or light-emitting diodes (LEDs) at very low, non-thermal doses. Discovered by Endre Mester in 1967 as having possible benefits in medicine for wound healing [20], it is now used to treat a range of conditions, including musculoskeletal conditions [21], and to promote wound healing [22]. It is a non-invasive treatment, applied using a hand-held device to the surface of the body. Devices typically deliver treatment to target tissues for 30 seconds to 60 seconds, at a wavelength of 600 nM to 700 nM and 780 nM to 1100 nM, with a power density range from 0.005 W/cm^2 to 5 W/cm^2. They may deliver continuous or pulsed light [23]. For people undergoing treatment for cancer, the device may be held inside (intraorally) or outside the mouth (extraorally), and applied by healthcare or dental professionals. Ideally, it is administered daily throughout cytoxic therapy.

Photobiomodulation has a photochemical effect. During injury to cells (caused by stress, such as illness or injury), the mitochondria produce nitric oxide, and there is a reduction in adenosine triphosphate (ATP [24]). One proposed mechanism of action is that photons from photobiomodulation dissociate inhibitory nitric oxide from the enzyme; this restores ATP, reduces oxidative stress, and enables faster recovery [23]. Other possible mechanisms of action relate to ion channels (transient receptor potential (TRP) channels), which are light-sensitive and open when stimulated during photobiomodulation therapy (this may promote histamine release at the site of the wound, thus enabling a wound-healing response), or relate to the effect of light on some molecules in cell-free systems; however, there is less evidence to support these proposed mechanisms [23].

Why it is important to do this review

This review is part of a series of Cochrane reviews of interventions for the prevention of oral mucositis in people receiving treatment for cancer, based on an original Cochrane review of all interventions [25]. The Cochrane reviews in this series have been divided according to these intervention categories relevant to oral mucositis, as guided by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO).

- Basic oral care
- Growth factors and cytokines
- Anti-inflammatory agents
- Antimicrobials, mucosal coating agents, anaesthetics, and analgesics
- Natural and miscellaneous agents
- Cryotherapy
- Laser and other light therapy

To date, the Cochrane Oral Health Group has published Cochrane reviews on cryotherapy, and growth factors and cytokines [26, 27].

Globally, 18.1 million people are diagnosed with cancer each year [28]. Although treatment options are, in part, dependent on the individual, those receiving radiotherapy to the head and neck and chemotherapy, along with people receiving haematopoietic stem cell transplantation or targeted therapy, are all at risk of developing oral mucositis. Whilst there is growing evidence for the effects of photobiomodulation on oral mucositis, robust synthesis of this evidence is not currently up-to-date. This review includes relevant studies on laser and light therapies included in an earlier Cochrane review [25], alongside an update of the current available evidence.

OBJECTIVES

To assess the effects of photobiomodulation for the prevention of oral mucositis in people undergoing treatment for head and neck cancers, other solid cancers, and haematological cancers.

METHODS

We will follow the Methodological expectations for Cochrane intervention reviews (MECIR) when conducting the review [29], and PRISMA 2020 for the reporting [30].

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with a parallel design. It is feasible to conduct cross-over study designs, and we will also include RCTs with these study designs in the review. Although less likely, it is also feasible to conduct cluster-RCTs for this topic, and we will include these types of studies if they meet other eligibility criteria.

We will exclude quasi-randomised trials (in which participants are allocated to groups using a non-random method, such as date of birth). We will also exclude split-mouth studies, because these designs are not practical for this condition, in which ulceration may not be evenly distributed within the mouth.

We will not limit the type of studies by setting.

We will include unpublished manuscripts and conference abstracts if they report sufficient information to meet the inclusion criteria for this review.

Types of participants

We will include people undergoing treatment for head and neck cancer, any other type of solid cancer, and haematological cancers. Treatments include chemotherapy, radiotherapy, a combination of chemotherapy and radiotherapy, or targeted therapies; these treatments may be in addition to surgery, or they may be used as conditioning therapy prior to haematopoietic stem cell transplantation. We will include studies with children and adults of any age.

In this review, we will report the evidence separately, according to three broad cancer types: head and neck cancer, other solid cancers, and haematological cancers.

It is possible that a study may include a mixed population (participants with different cancer types). If data for these different types are not reported separately in the study report, we will contact study authors to request data; if we are unable to obtain them, we will report data for these mixed populations separately in the review.

Types of interventions

We will include photobiomodulation therapy used to prevent oral mucositis that uses red or near-red light, such as low-level light or laser therapy (LLLT), as well as light-emitting diodes (LEDs) or visible light therapy. We will include studies regardless of protocols for photobiomodulation application in the studies (i.e. type of device, wavelength, power and power density; timing (within cancer treatment journey), intraoral or extraoral application, duration and frequency of therapy).

We will compare photobiomodulation with no treatment or sham therapy (inactive control), or with any alternative prophylactic treatment (active control). We will also include comparisons of different approaches to photobiomodulation application (active controls).

Comparisons are based on the interventions grouped as follows:

- photobiomodulation;
- inactive control: no treatment, sham therapy;
- active control: an alternative prophylactic intervention (i.e. given to prevent oral mucositis, such as cryotherapy or anti-inflammatory agents, and excluding any types of photobiomodulation);
- active control: photobiomodulation using an alternative application approach (such as different wavelengths, power energy density, exposure time, and frequency of exposure).

When a study compares photobiomodulation with different application approaches, we will treat the control as the group that uses application approaches that are closest to the recommended parameters in the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines for photobiomodulation [7].

We will exclude interventions with multiple components, in which it is not possible to determine the effectiveness of photobiomodulation (e.g. cryotherapy with photobiomodulation versus sham therapy).

Outcome measures

Critical outcomes

- **Mucositis** - presence of mucositis using a recognised measurement tool (World Health Organization (WHO) scale for oral mucositis [31]; National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (specific for oral mucositis [32]); Oral Mucositis Assessment Scale (OMAS [33]). We will collect data on the number of people with mucositis, based on the maximum score of oral mucositis experienced by each participant during the study period. We will use thresholds of severe, moderate to severe mucositis, and any mucositis as described in Measures of treatment effect, and we will present the data separately for each of these thresholds.
- **Adverse effects** - any event (other than oral mucositis), for which the causal relation between photobiomodulation and the event is at least a reasonable possibility

Important outcomes

- **Interruptions to cancer treatment** - measured as either the prevalence (the number of people with interruptions to cancer treatment), or the severity (number of days of treatment interruption). For this outcome, we are interested in interruptions to cancer treatment as a consequence of oral mucositis.
- **Oral pain** – measured using a validated pain scale, such as a visual analogue score (VAS)

- **Opioid use** – the number of days of opioid use (including topical and non-topical opioids)
- **Ability to eat a normal diet** – measured according to whether a person is unable to eat soft food or requires invasive nutritional support (parenteral or enteral feeding), as either the prevalence (the number of participants unable to eat soft food, or using invasive nutritional support) or severity (the number of days in which people are unable to eat soft food, or use invasive nutritional support)
- **Quality of life** – measured using an appropriate validated scale. If data are reported within a study using more than one measurement instrument, we will prioritise data measured using Functional Assessment of Cancer Therapy (FACT [34]) subscales (appropriate to relevant cancer types), followed by EQ-5D [35], and then the 36-item Short Form Health Survey (SF-36 [36]).
- **Duration of hospital stay** – measured as number of days in hospital during the study period
- **Number of days during which oral medication could not be taken**

Except for the outcome of interruptions to cancer treatment, these important outcomes are taken from a core outcome set developed for the prevention and treatment of oral mucositis [37]. We modified one outcome (ability to soft food) from this core outcome set to also incorporate a measure of invasive nutritional support. People who had bone marrow transplantation and experienced oral mucositis were included in the development of this core outcome set. We expanded the time frame of measurement of these outcomes to include people who may experience oral mucositis symptoms for longer (because of differences in their cancer treatment). Therefore, we will collect data for these outcomes measured within three months of cancer treatment.

If a study uses multiple measurement tools for reporting an outcome, we will select data from the tool that is most commonly used in the review's other included studies.

Search methods for identification of studies

Electronic searches

Using tailored search strategies, we will search the following electronic databases for relevant trials.

- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library
- MEDLINE Ovid (1946 to present)
- Embase Ovid (1980 to present)
- CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature; 1937 to present)

There will be no limitation based on language or publication type. In MEDLINE, we will combine subject-specific terms with the sensitivity-maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (38). We will adapt the MEDLINE search strategy to use in the other listed electronic databases (Supplementary material 1). We based the terms for cancer and oral mucositis on a previous search strategy developed by a former Cochrane Oral Health group Information Specialist [26].

We will search the following trials registries.

- The World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (https://clinicaltrials.gov/)

Searching other resources

We will search for further studies in the reference lists of included studies and relevant systematic review identified in the results of the electronic database searches. In addition, we will check that none of the identified included studies have been retracted due to error or fraud, using Retraction Watch (retractionwatch.com/).

Data collection and analysis

Selection of studies

We will import references identified from electronic sources to Covidence, and will use this software to select eligible studies for this review (39). Two review authors, independently and in duplicate, will screen the titles and abstracts of all references retrieved from electronic searches for possible inclusion in the review. We will obtain the full-text copies of potentially eligible articles, which we will evaluate for inclusion. We will resolve any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

Data extraction and management

Two review authors, independently and in duplicate, will extract study characteristics and quantitative data from each included study, using a data extraction form in Covidence [39], which we will initially pilot on a small sample of studies (10% of the included studies). We will contact study authors by email for clarification or missing data when necessary and feasible. We will resolve any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

We will record the following information for each included study.

- Methods: study design, study dates, comparison group (intervention; type of cancer treatment)
- Participants: inclusion/exclusion criteria, type of cancer and treatment regimen, study centre(s) and country, number randomised to groups, number of losses and number analysed at final follow-up, baseline characteristics of participants in each group (age, sex, and other PROGRESS-Plus characteristics [40], (also see 'Equity-related assessment', below), types of cancer and treatment per group (if mixed populations), other relevant prognostic variables as defined in individual studies)
- Interventions: details of photobiomodulation therapy (type of device, wavelength, power and power density; timing (within cancer treatment journey), intraoral or extraoral application, duration and frequency of therapy); details of comparison therapy (as applicable)
- Outcomes: review outcomes (to include measurement tool and time point of measurement), quantitative outcome data for outcomes listed in Critical outcomes and Important outcomes (e.g. number of events or mean scores per group, and total number analysed per group); other outcomes reported by study authors. For cross-over studies, we will only collect data for the first study period in order to reduce the risk of carry-over effects.

- Other: funding sources and study author declarations of interest; study registration details; any other relevant study information

Risk of bias assessment in included studies

Two review authors, independently and in duplicate, will assess the risk of bias in each included study using RoB 2 (41); we will also be guided by Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (42). We will resolve any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

RoB 2 covers the following five domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

If we identify any cluster-RCTs, we will use the most up-to-date modified RoB 2 tools for this RCT design (Risk of bias tools - RoB 2 tool). Because we will only use data from the first study period in cross-over RCTs, we will assess the risk of bias in these studies as if they are parallel designs, using the standard RoB 2 tool.

We will prioritise assessment of risk of bias for the study results of the critical outcomes in this review: mucositis (moderate to severe mucositis, severe mucositis, and any mucositis); and adverse effects.

We are interested in quantifying the effect of assignment to the intervention at baseline, regardless of whether the interventions were received as intended (the intention-to-treat (ITT) effect). To implement RoB 2, we will use the RoB 2 Excel tool (available at www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). For each domain, we will use the signalling questions provided by the RoB 2 tool, answering yes, probably yes, probably no, no, or no information.

We will use this process to reach a risk of bias judgement for each result of low risk of bias, some concerns, or high risk of bias. Generally, the overall risk of bias score for a result is based on the least favourable assessment made for any of the domains. However, if some concerns arise in multiple domains, we will assign an overall high risk of bias judgement for that result. The RoB 2 tool automatically generates a judgement regarding bias for each domain and overall bias. However, we will check these automatically-generated judgements and amend them if necessary [42].

Measures of treatment effect

For dichotomous data, we will express the effect estimate as a risk ratio (RR) with 95% confidence intervals (CI). We anticipate that mucositis may be measured using an ordinal scale (e.g. using a multiple-point scale of mucositis with pre-existing categories of severity). In this case, we will dichotomise the data at three thresholds: moderate to severe mucositis, severe mucositis, and any mucositis. For any mucositis, we will collect data for incidences of mild, moderate, and severe mucositis. Because we anticipate this outcome will be measured using different scales, in the published review, we will describe how we dichotomised each measurement scale. We plan to split these data so that each category is sufficiently homogenous between measurement scales. If scales are not obviously grouped using terms for severity (i.e. moderate to severe and severe), we will discuss, as a whole review team, and agree appropriate cutoffs to group the data.

For continuous data, for which studies report data using the same measurement tool and scale, we will express the effect estimate as mean difference (MD) with 95% CIs. If studies report data using different scales, we will report the standardised mean difference (SMD) and its associated 95% CI. However, in this case, we will also re-express these data as an MD of the most commonly used scale in the meta-analysis (ideally, this will also be the scale most familiar to users of the review). We will be guided by Section 15.5.3.2 of the *Cochrane Handbook* (42).

Unit of analysis issues

We anticipate the individual participant will be the unit of analysis for this review. If studies include more than two study groups, we will meta-analyse data using approaches that avoid double-counting of participants (Chapter 23 of the *Cochrane Handbook* [42]). If intervention (or control) groups are sufficiently similar (i.e. in the same main comparison group), we will combine study groups to create a single pair-wise comparison. Alternatively, for continuous data, we will split the 'shared' group into two or more groups with smaller sample sizes, and include two or more independent comparisons in the meta-analysis.

If cluster-randomised trials are included, we will use the cluster (e.g. a healthcare unit or centre) as the unit of analysis. If studies adjust data for the clustering effect, we will use adjusted data reported by the study authors. Otherwise, we will calculate effective sample sizes for each study group, using guidance in Chapter 23 of the *Cochrane Handbook* [42]. For cross-over studies, we will only use data from the first study period; therefore, there will be no unit of analysis issues related to this study design.

Dealing with missing data

We will contact study authors of the selected studies when methodology or other information is unclear or missing. In the review, we will distinguish between published data and data sourced from personal communication. If we are unable to source additional outcome data for missing participants, we will include only the available data in the meta-analysis. If data are missing for continuous data (e.g. missing SDs), we will use methods described in Section 6.5.2 of the *Cochrane Handbook* [43].

Reporting bias assessment

We will seek prospective clinical trials registration or a prespecified analysis plan or protocol for all included studies, and use this information to assess bias in the selection of the reported result. We will also assess whether studies selectively reported findings of a particular outcome measurement or a particular analysis. We will evaluate this information during the risk of bias assessment (Risk of bias assessment in included studies). We will assess the risk of bias due to missing evidence using the ROB-ME tool (https://methods.cochrane.org/bias/resources/rob-me). Two review authors will independently conduct these bias assessments, reaching consensus through discussion, and involving a third review author to resolve any disagreements.

We will generate a funnel plot for meta-analyses including more than 10 studies (of different sample sizes), as a means of displaying small-study effects [42]. If we note asymmetry when we visually inspect the funnel plot, we will carry out tests, using Egger 1997 for continuous outcomes and Rűcker 2008 for dichotomous outcomes [44, 45]. Although asymmetry may indicate a risk of publication bias (possible non-reporting of studies), we note that there are other possible reasons for asymmetry in funnel plots [42].

Synthesis methods

We will conduct meta-analyses of studies that have sufficiently similar participants, interventions, comparisons, and outcome measures. We will pool studies regardless of the overall risk of bias judgement. We will use the population characteristics in each study (see Types of participants) to categorise the study into one of the review comparison groups.

We will include studies in analyses for the following comparisons, with separate analyses according to three cancer types (head and neck cancer, other solid cancers, and haematological cancers).

- Photobiomodulation versus no treatment or sham therapy
- Photobiomodulation versus an alternative intervention given to prevent oral mucositis
- Photobiomodulation versus photobiomodulation (where different approaches to application are used in each group)

It is feasible that a study may include (or we obtain from the study authors) separate data for mixed populations; thus, a subset of participants from a study may be included in more than one comparison group.

We will combine data from more than one study using random-effects models to allow for clinical variation between study populations. Using Stata [46], we will use the inverse-variance method for analyses, using restricted maximum likelihood (REML) or DerSimonian and Laird for the between-study variance estimator according to characteristics, such as number of studies. We will use the level of observed heterogeneity and the number of studies in the analyses to choose between Hartung-Knapp-Sidik-Jonkman or Wald approaches to calculate CIs. If RCTs report data as effect estimates and 95% CIs (without numerical data per group), we will add these data to meta-analyses using the generic inverse variance (GIV) method. For cluster-RCTs, we will use adjusted data as reported by study authors, which we will add to meta-analyses using GIV; otherwise we will calculate effective sample sizes (see Unit of analysis issues). We will present the quantitative results of any analyses in forest plots, and we will summarise the results in the review report.

We will assess statistical heterogeneity in the results of the meta-analyses by visually inspecting the point estimates and CIs in the forest plots. Lack of overlap of CIs may indicate heterogeneity. We will also assess statistical heterogeneity using Cochran's test for heterogeneity and the I^2 statistic. For interpretation of the amount of statistical heterogeneity, we will use the thresholds outlined in the *Cochrane Handbook* [47].

If data are not amenable to meta-analysis, we will synthesise the results of studies according to the Synthesis Without Meta-analysis (SWiM) guidelines [48].

Investigation of heterogeneity and subgroup analysis

If sufficient data are available, we will use formal tests for subgroup interactions to evaluate whether there are different results of the meta-analyses between children and adult participants, the types of cancer treatment that participants received, and whether photobiomodulation was applied intra- or extraorally. We will undertake these subgroup analyses regardless of statistical heterogeneity in the pooled effect.

We will conduct subgroup analysis on study-level variables (i.e. each study will only be included in one subgroup). However, if a study includes mixed characteristics (e.g. inclusion of adults and children), and separate data are available for participants in these groups, we will include subsets of participants in each subgroup. We will calculate statistical tests for subgroup interactions using Stata [46].

Equity-related assessment

We will collect participant characteristics according to PROGRESS-Plus [40]. These characteristics relate to place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, social capital, personal characteristics associated with disability, features of relationships, and time-dependent relationships. We will report these in the tables of study characteristics. We do not plan to formally explore equity-related characteristics in this review. However, we will note any observations of equity-related study characteristics, and describe these in the review in relation to the applicability and generalisability of the review findings.

Sensitivity analysis

We will evaluate the robustness of a meta-analysis on decisions taken during the review process as follows.

- We will exclude studies that we judged to have an overall high risk of bias.
- We will exclude studies that we judged to be at risk of bias due to missing evidence as part of the ROB-ME assessment.
- If a meta-analysis includes one very large study and several small studies, we will re-analyse data using a fixed-effect model.
- We will exclude studies for which we have imputed missing SDs.
- We will remove any study-level summary statistics that are obvious outliers (identified from visual inspection of the data).

We will compare the results of sensitivity analysis with the primary analysis. We will report any effect estimates that indicate a different interpretation of the effect (e.g. that differ from the primary analysis in size or direction of effect).

Certainty of the evidence assessment

We will use the GRADE methodology to assess the certainty of the body of evidence associated with the following critical outcomes in the review [49]:

- Severe mucositis
- Moderate to severe mucositis
- Any mucositis
- Adverse effects

The GRADE approach assesses the certainty of a body of evidence based on the extent to which we can be confident that an estimate of effect, or association reflects the item being assessed. Evaluation of the certainty of a body of evidence considers within-study risk of bias (study limitations), directness of the evidence (indirectness), heterogeneity of the data (inconsistency), precision of the effect estimates (imprecision), and risk of publication bias. We will use the overall risk of bias judgements from our ROB 2 assessments when assessing the within-study risk of bias. The certainty of the evidence could be high, moderate, low, or very low, when downgraded by one or two levels, depending on the presence and extent of concerns in each of the five GRADE domains. We will use footnotes to describe reasons for downgrading the certainty of the evidence for each outcome, and we will use these judgements when drawing conclusions in the review.

Two review authors will independently assess the certainty of the evidence and reach consensus through discussion, consulting a third review author in the event of any disagreement.

We will construct summary of findings tables for the following three comparisons.

- Photobiomodulation to prevent oral mucositis compared with no treatment or sham treatment in people undergoing treatment for head and neck cancers
- Photobiomodulation to prevent oral mucositis compared with no treatment or sham treatment in people undergoing treatment for solid cancers (other than head and neck cancers)
- Photobiomodulation to prevent oral mucositis compared with no treatment or sham treatment in people undergoing treatment for haematological cancers

We will use GRADEpro GDT software to construct these tables [50].

Consumer involvement

Why are you involving people? It is important for us to listen to people who have experienced oral mucositis as a result of treatment for cancer. This allows us to make sure our research is relevant to the right people. Involving people with lived experience will improve the quality of our research, and will improve how our findings are shared with the right people.

Who will be involved? In our review author team, we included an Oral Medicine Lecturer who has lived experience of oral mucositis as a result of treatment for cancer. This author drew from personal experience, as well as clinical knowledge, when developing this protocol. When planning outcomes for this review, we used a core outcome set that was developed with consumer involvement [37].

What do you plan to do, and when will you do it? We will co-produce the review with our review author who has lived experience. We will also identify potential consumers from our wider clinical networks, and seek to involve these consumers in the interpretation of the evidence and presentation of the results. We will engage with consumers in preparation of the plain language summary. We will also seek consumer opinion about using photobiomodulation for prevention of oral mucositis, and any implications for future research identified from the review findings; we will include this information in the final report.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016068.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

Acknowledgements

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Toby Lasserson, Deputy Editor-in-Chief, Cochrane
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sara Hales-Brittain, Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Jacob Hester, Central Editorial Assistant
- Copy Editor (copy editing and production): Victoria Pennick, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision):
  - Alan Roger Santos-Silva, DDS, MSc, PhD, FAAOM Oral Diagnosis Department, Piracicaba Dental School, State University of Campinas, Brazil (clinical/content review),
  - Dinesh Rokaya (Chulalongkorn University; consumer review),
  - Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review),
  - Jo Platt, Central Editorial Information Specialist (search review).
  - Pr Rene-Jean BENSADOUN, Centre de Haute Energie, Nice (France), WALT President 2021/2024 (clinical/content review)
  - Prof. Yehuda Zadik, Department of Oral Medicine, and Saligman Clinics, Faculty of Dental Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel (clinical/content review)

Contributions of authors

Conception of the review: PR
Design of the protocol: SL, PR, ED, AMG, MG, LO'M, TW, HW
Co-ordination of the protocol: SL
Writing the protocol: SL, PR, ED, AMG, MG, LO'M, TW, HW

Declarations of interest

SL is the former Deputy Co-ordinating Editor of the Cochrane Bone, Joint and Muscle Trauma group; they were not involved in the editorial process for this protocol. No commercial or non-commercial interests relevant to this review.

PR is the Deputy Co-ordinating Editor of the Cochrane Oral Health group; they were not involved in the editorial process for this protocol. No commercial or non-commercial interests relevant to this review.

ED has no commercial or non-commercial interests relevant to this review.

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Registration and protocol

Cochrane approved the proposal for this review in November 2023.

Data, code and other materials

Data sharing not applicable to this article as it is a protocol, so no datasets were generated or analysed.

REFERENCES

1. Berger K, Schopohl D, Bollig A, Strobach D, Rieger C, Rublee D, et al. Burden of oral mucositis: a systematic review and implications for future research. *Oncology Research and Treatment* 2018;**41**(6):399-405. [DOI: 10.1159/000487085]

2. Brown TJ, Gupta A. Management of cancer therapy-associated oral mucositis. *JCO Oncology Practice* 2020;**16**(3):103-9. [DOI: 10.1200/jop.19.00652]

3. Pulito C, Cristaudo A, Porta C, Zapperi S, Blandino G, Morrone A, et al. Oral mucositis: the hidden side of cancer therapy. *Journal of Experimental & Clinical Cancer Research* 2020;**39**(1):210. [DOI: 10.1186/s13046-020-01715-7]

4. Scully C, Sonis S, Diz PD. Oral mucositis. *Oral Diseases* 2006;**12**(3):229-41. [DOI: 10.1111/j.1601-0825.2006.01258.x]

5. Qutob AF, Gue S, Revesz T, Logan RM, Keefe D. Prevention of oral mucositis in children receiving cancer therapy: a systematic review and evidence-based analysis. *Oral Oncology* 2013;**49**(2):102-7. [DOI: 10.1016/j.oraloncology.2012.08.008]

6. Bell A, Kasi A. Oral Mucositis. (Updated 29 May 2023). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023. Available from https://www.ncbi.nlm.nih.gov/books/NBK565848/.

7. Elad S, Cheng KK, Lalla RV, Yarom N, Hong C, Logan RM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2020;**126**(19):4423-31. [DOI: 10.1002/cncr.33100]

8. Al-Rudayni AH, Gopinath D, Maharajan MK, Menon RK. Impact of oral mucositis on quality of life in patients undergoing oncological treatment: a systematic review. *Translational Cancer Research* 2020;**9**(4):3126-34. [DOI: 10.21037/tcr.2020.02.77]

9. Jensen SB, Peterson DE. Oral mucosal injury caused by cancer therapies: current management and new frontiers in research. *Journal of Oral Pathology & Medicine* 2014;**43**(2):81-90. [DOI: 10.1111/jop.12135]

10. Miller M, Kearney N. Oral care for patients with cancer: a review of the literature. *Cancer Nursing* 2001;**24**(4):241-54. [DOI: 10.1097/00002820-200108000-00001]

11. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiotherapy and Oncology* 2003;**66**(3):253-62. [DOI: 10.1016/s0167-8140(02)00404-8]

12. Peterson DE, Srivastava R, Lalla RV. Oral mucosal injury in oncology patients: perspectives on maturation of a field. *Oral Diseases* 2015;**21**(2):133-41. [DOI: 10.1111/odi.12167]

13. Hong CH, Gueiros LA, Fulton JS, Cheng KK, Kandwal A, Galiti D, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. *Supportive Care in Cancer* 2019;**27**(10):3949-67. [DOI: 10.1007/s00520-019-04848-4]

14. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004;**100**(9 Suppl):1995-2025. [DOI: 10.1002/cncr.20162]

15. Mougeot JC, Stevens CB, Morton DS, Brennan MT, Mougeot FB. Oral microbiome and cancer therapy-induced oral mucositis. *Journal of the National Cancer Institute. Monographs* 2019;**2019**(53):lgz002. [DOI: 10.1093/jncimonographs/lgz002]

16. Sonis ST. Mucositis: the impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncology* 2009;**45**(12):1015-20. [DOI: 10.1016/j.oraloncology.2009.08.006]

17. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. *Frontiers in Oncology* 2017;**7**:89. [DOI: 10.3389/fonc.2017.00089]

18. Elting LS, Chang YC. Costs of oral complications of cancer therapies: estimates and a blueprint for future study. *Journal of the National Cancer Institute. Monographs* 2019;**53**:lgz010. [DOI: 10.1093/jncimonographs/lgz010]

19. Rodrigues-Oliveira L, Kowalski LP, Santos M, Marta GN, Bensadoun RJ, Martins MD, et al. Direct costs associated with the management of mucositis: a systematic review. *Oral Oncology* 2021;**118**:105296.

20. Hamblin MR. Photobiomodulation or low-level laser therapy. *Journal of Biophotonics* 2016;**9**(11-12):1122-4. [DOI: 10.1002/jbio.201670113]

21. Cotler HB, Chow RT, Hamblin MR, Carroll J. The use of low level laser therapy (LLLT) for musculoskeletal pain. *MOJ Orthopedics & Rheumatology* 2015;**2**(5):00068. [DOI: 10.15406/mojor.2015.02.00068]

22. Chittoria RK, Kumar SH. Low-level laser therapy (LLLT) in wound healing. In: Shiffman M, Low M. Recent Clinical Techniques, Results, and Research in Wounds. Springer International Publishing AG, 2018. https://zero.sci-hub.se/6880/faa871108f52e88d49d75e1852872a1d/chittoria2018.pdf. [DOI: 10.1007/15695_2017_89]

23. de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. *IEEE Journal of Selected Topics in Quantum Electronics* 2016;**22**(3):7000417. [DOI: 10.1109/jstqe.2016.2561201]

24. Hamblin MR. Mechanisms and mitochondrial redox signaling in photobiomodulation. *Photochemistry and Photobiology* 2018;**94**(2):199-212. [DOI: 10.1111/php.12864]

25. Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews* 2011, Issue 4. Art. No: CD000978. [DOI: 10.1002/14651858.CD000978.pub5]

26. Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG. Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No: CD011552. [DOI: 10.1002/14651858.CD011552.pub2]

27. Riley P, Glenny AM, Worthington HV, Littlewood A, Fernandez Mauleffinch LM, Clarkson JE, et al. Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No: CD011990. [DOI: 10.1002/14651858.CD011990.pub2]

28. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians* 2021;**71**(3):209-49. [PMID: 33538338]

29. Higgins JP, Lasserson T, Thomas J, Flemyng E, Churchill R. Methodological expectations of Cochrane intervention reviews. Cochrane: London, Version August 2023. Available from https://community.cochrane.org/mecir-manual.

30. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. [DOI: 10.1136/bmj.n71]

31. WHO: World Health Organization. Handbook for reporting results of cancer treatment. In: WHO Offset Publications. Vol. **48**. Geneva, Switzerland: World Health Organization, 1979:15-22.

32. US Department of Health and Human Services (US DHHS). Common Terminology Criteria for Adverse Events v5.0 (CTCAE); November 2017. ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

33. Sonis ST, Eilers JP, Epstein JB, LeVeque FG, Liggett WHJr, Mulagha MT, et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer* 1999;**85**(10):2103-13. [DOI: 10.1002/(sici)1097-0142(19990515)85:10<2103::aid-cncr2>3.0.co;2-0]

34. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of Clinical Oncology* 1993;**11**(3):570-9. [DOI: 10.1200/JCO.1993.11.3.570]

35. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199-208.

36. RAND Corporation. 36-Item Short Form Survey (SF-36). Available from https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html 1992;**(accessed 19 July 2024)**.

37. Bellm LA, Cunningham G, Durnell L, Eilers J, Epstein JB, Fleming T, et al. Defining clinically meaningful outcomes in the evaluation of new treatments for oral mucositis: oral mucositis patient provider advisory board. *Cancer Investigation* 2002;**20**(5-6):793-800.

38. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, et al. Technical Supplement to Chapter 4: Searching for and selecting studies (last updated September 2024). In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from https://www.training.cochrane.org/handbook.

39. Covidence. Version accessed 3 November 2023. Melbourne, Australia: Veritas Health Innovation, 2023. Available at https://covidence.org.

40. O'Neill J, Tabish H, Welch V, Petticrew M, Pottie K, Clarke M, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. *Journal of Clinical Epidemiology* 2014;**67**(1):56-64. [PMID: 24189091]

41. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

42. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5 (updated August 2024). Cochrane, 2024. Available from https://www.training.cochrane.org/handbook.

43. Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect (last updated August 2023). In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from https://www.training.cochrane.org/handbook.

44. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

45. Rűcker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analysis with binary outcomes. *Statistics in Medicine* 2008;**27**(5):746-63.

46. Stata. Version 15. College Station, TX, USA: StataCorp, 2024. Available at https://www.stata.com.

47. Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from https://www.training.cochrane.org/handbook.

48. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis

(SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**16**(368):l6890. [DOI: 10.1136/bmj.l6890]

49. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence (last updated August 2023). In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane, 2024. Available from https://www.training.cochrane.org/handbook.

50. GRADEpro GDT. Version accessed 3 November 2023. Hamilton (ON): McMaster University (developed by Evidence Prime), 2023. Available at gradepro.org.