ORIGINAL RESEARCH

Low-level Laser Therapy in the Management of Oral Mucositis Induced by Radiotherapy: A Randomized Double-blind Clinical Trial

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Abstract

Aim: The present study evaluated the effect of LLLT at red and infrared wavelengths associated with therapeutic measures from the Mucositis Study Group of the Multinational Association of Supportive Care of Cancer and International Society of Oral Oncology (MASCC/ISOO) for preventing and treating RT-induced oral mucositis (OM).

Materials and methods: For the study, 80 subjects diagnosed with head and neck cancer (HNC) undergoing treatment were randomized into three groups to apply different photobiomodulation protocols for 42 days, as follows: Group I—LLLT of 660 nm; Group II—LLLT of 810 nm; and Group III—association of wavelengths of 660 and 810 nm. The treatments were performed by properly trained professionals and with equipment calibrated for the intervention.

Results: Different OM scores were noted for the groups studied, and the third group had lower scores than Groups I and II ($p = 0.012$). No difference was noted in the pain score analyzing the groups ($p = 0.49$).

Conclusion: The LLLT was effective for OM lesions in individuals treated with radiotherapy associated or not with chemotherapy. When combined, the red and infrared lasers reduce OM scores.

Clinical significance: OM is one of the main adverse effects of antineoplastic therapy in head and neck cancer patients. The evidence supporting the validity of LLLT for OM can improve patients' quality of life.

Keywords: Laser therapy, Oral mucositis, Radiotherapy.

The Journal of Contemporary Dental Practice (2022): 10.5005/jp-journals-10024-3277

Introduction

Cancer incidence and mortality are growing rapidly worldwide.[1–4] Radiotherapy (RT) is one of the main treatment modalities used for more than 50% of all cancer patients,[5] representing the main curative option for advanced tumors in the case of head and neck cancer (HNC).[6] The combined therapy involving RT and chemotherapy (CT) has represented an effective alternative for the treatment of HNC.[7,8]

Even from a multimodal approach, the treatment of HNC patients is still liable to an unsatisfactory clinical result, with approximately 50% of local recurrence in 3 years and a relatively high rate of serious toxicity related to RT.[8] This is because, although the main objective of cancer treatments such as RT and CT is to destroy cancer cells, they do not act selectively, working on both malignant and normal cells.[9,10]

Oral mucositis (OM) is one of those damages occurring in the lining of the oral mucosa,[11] representing an important adverse effect observed in HNC patients undergoing radio- and chemotherapy.[9] This condition is characterized by atrophic erythematous and painful lesions in its mildest form and ulcerative lesions that penetrate the submucosa in more severe forms.[12,13]

OM-related complaints consist of pain when swallowing, reduced feeding, increased opioid consumption, in addition to increased need for parenteral nutrition, which may lead to unwanted interruptions in RT.[14,15] Although OM cannot be completely avoided, many preventive and treatment strategies can help to decrease its incidence, severity, and duration.[16] Clinical practice guidelines to prevent OM secondary to cancer therapy have been published to maintain oral hygiene during the treatment.[17]

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How to cite this article: Kuhn-Dall'Magro A, Zamboni E, Fontana T, *et al*. Low-level Laser Therapy in the Management of Oral Mucositis Induced by Radiotherapy: A Randomized Double-blind Clinical Trial. J Contemp Dent Pract 2022;23(1):31–36.

Source of support: Nil

Conflict of interest: None

Among other supportive care measures available, low-level laser therapy (LLLT), also known as photobiomodulation (PBM), has shown a significant promise.[18] The PBM includes a wide range of nonionizing light sources such as lasers and light-emitting diodes (LEDs) in the visible spectrum of red and infrared lights, at very low nonthermal doses.[15,19] This modality produces a biostimulant effect within the cells and analgesic and anti-inflammatory effects caused by the increase in cell tropism and microvascular density in the local connective tissue, accelerating wound healing and reducing postoperative edema.[7,19,20]

So, this research aimed to observe the effectiveness of three laser protocols and established therapeutic measures[17] for preventing and treating OM induced by head and neck RT, considering the degrees of OM with the scale proposed by the World Health Organization[21] and assessing pain with a visual analog scale (VAS).

Materials and Methods

Ethical Considerations

This study is a randomized, double-blind clinical trial with three parallel groups, evaluated by the Scientific Committee of São Vicente de Paulo Hospital (HSVP) in Passo Fundo, Rio Grande do Sul, Brazil, and the Research Ethics Committee of the University of Passo Fundo (UPF), Rio Grande do Sul, Brazil (CAAE 53617615.5.0000.5342). Moreover, the study was registered on the REBEC Platform. The patients signed an informed consent form (ICF) and all researchers involved in this study received training through theoretical and practical classes before starting the intervention and data collection.

Participants

The selection and treatment of patients elected to participate in this research occurred between November 2015 and November 2017. During this period, patients diagnosed with HNC undergoing treatment at the HSVP were invited to participate in the study. One-hundred and seven participants were considered eligible for the study. However, after the initial assessment, the estimated sample size was 80 volunteer patients who met the following criteria: be an adult (18 years or older), to be about to start radiotherapy for the treatment of HNC, associated or not to CT, present conditions to receive the treatments proposed for this study, and have signed the ICF.

Individuals with impediments, such as stopping of RT for 7 days or more, or locomotion difficulty, and patients who refused to apply PBM or who did not respect the proposed protocol were excluded from the research.

Adequacy and Oral Hygiene

All patients underwent a dental evaluation, receiving instructions according to the latest MASCC/ISOO consensus.[17] These guidelines were delivered in writing in a care booklet and ratified daily for the patients and/or their caregivers. Oral hygiene kits were distributed to all participants and included a soft toothbrush, dental floss, artificial saliva spray bottle, Benzydamine (Flogoral™ spray), low abrasive toothpaste, and alcohol-free fluoridated antiseptic solution to apply every 12 hours.

Septic teeth were removed before starting the treatment with RT, as requested by the radiotherapist. Oral hygiene was monitored daily by the research team.

Treatment Application Parameters and Logistics

- Randomization of patients: The patients were randomized by a draw and allocated into three blocks respecting the therapeutic protocol, as follows: red laser (Group I—G1); infrared laser (Group II—G2); and infrared and red lasers combined (Group III—G3).
- Laser application period and application sites: The period of application of the LLLT treatment was 42 days for each patient selected for the study, occurring during your RT treatment period. In each group, daily laser applications were performed throughout the RT period. All subjects received daily, at 30 points (Fig. 1),[22] the treatment with LLLT using a Therapy XT device (DMC Equipamentos, São Carlos, São Paulo, Brazil) properly regulated. Each application of LLLT lasted 30 minutes.
- Laser parameters applied to each group: In G1 was applied a laser of 660 nm (red), adjusted to 100 mW and 6 J/cm^2, daily, during the RT. G2 received the laser of 810 nm (infrared) adjusted to 100 mW and 6 J/cm^2, daily during the RT treatment. For G3, lasers with 660 nm (red) + 810 nm (infrared) were applied simultaneously, with 100 mW and 6 J/cm^2, daily during the RT treatment.

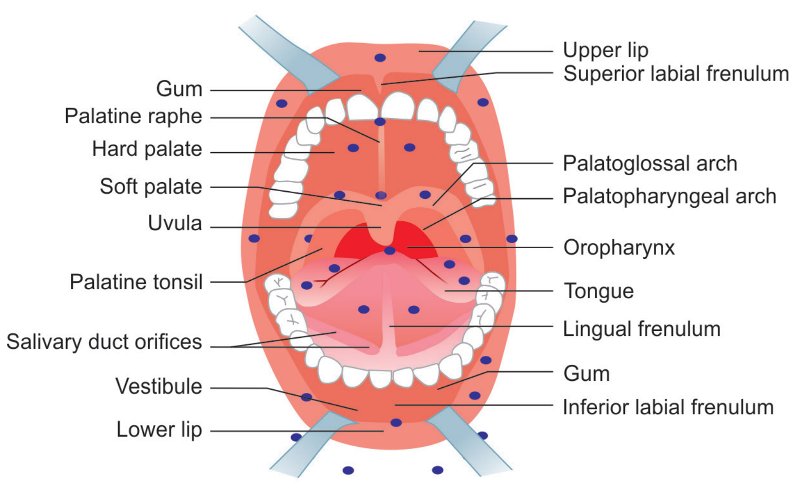


Fig. 1: Laser application points (adapted from Kuhn et al.[22])

- Patient's evaluation: The subjects of all groups were monitored by a blind clinician. The degree of OM was measured according to the WHO scale until day 42 after the start of the intervention, three times a week (every Monday, Wednesday, and Friday). The pain degree was measured daily using the VAS for the same time. Graphically, the OM and pain results in the present study are presented on days 0, 7, 14, 21, 28, 36, and 42. Personal data were collected in specific worksheets.

Statistical Analysis

The data were organized in an Excel™ spreadsheet for Windows (version 2013, Excel, Microsoft Inc., Redmond, Washington, USA) and subjected to statistical analysis with the SPSS software (IBM Inc., Chicago, Illinois, USA), considering $\alpha = 5\%$. Generalized estimating equations (GEE) were used to compare OM and pain scores between the groups.

Results

In the present study, the initial sample consisted of 107 adult patients of both sexes referred to head and neck RT at the HSVP of Passo Fundo, Rio Grande do Sul, Brazil. However, due to clinical complications that prevented the study, 27 patients were excluded from the study and only 80 completed the follow-up period. The aforementioned complications were related to interruption of RT for more than a week, difficulty in coordination and/or locomotion that prevented laser application and poor adherence to the proposed oral hygiene. Thus, the final sample of this study was 26 patients in G1, 25 in G2, and 29 in G3 (Flowchart 1).

The average age of the patients was 68 years. Sixty-seven patients (84%) were men and 13 (16%) were women. No differences were noted in the distribution of patients between G1, G2, and G3, reviewing characteristics such as concomitant treatment of RT/CT ($p = 0.62$), age ($p = 0.79$), and sex ($p = 0.18$).

The sites most affected by OM were the cheek mucosa (68%), the lateral and ventral regions of the tongue (52%), and lips (30%). Applications of LLLT were made on sites affected by oral mucositis, being well tolerated and showing no adverse side effects attributable to its use.

Figure 2 shows the absolute frequency of OM scores between the groups after 7, 14, 21, 28, 36, and 42 days of intervention. Considering that the objective of the present study was to evaluate the degrees of OM and pain in patients undergoing RT of the head and neck under the application of lasers of different wavelengths, the results indicate a significant difference in the OM score between G1, G2, and G3, with G3 (associated lasers) showing lower MO scores ($p = 0.012$) than G1 and G2. There was no difference in the pain score (VAS) between the groups ($p = 0.49$). The pain reported between the three groups was low, which allowed maintaining the RT sequence (Fig. 3).

Discussion

Radiotherapy (RT) may result in debilitating side effects that negatively affect the functional capabilities and quality of life of

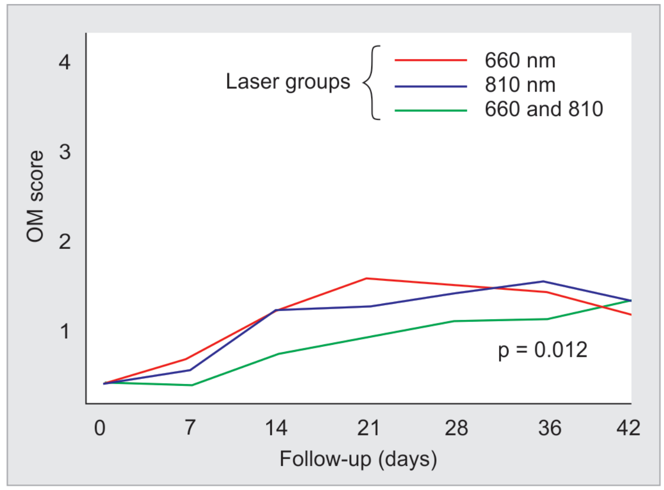


Fig. 2: OM throughout the treatment. The results showed a significant difference in OM graduation between the three groups, with Group III presenting lower OM scores ($p = 0.012$) than Groups I and II

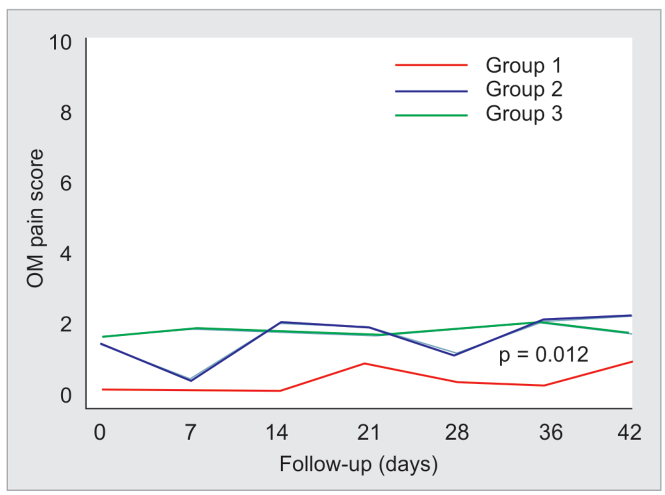
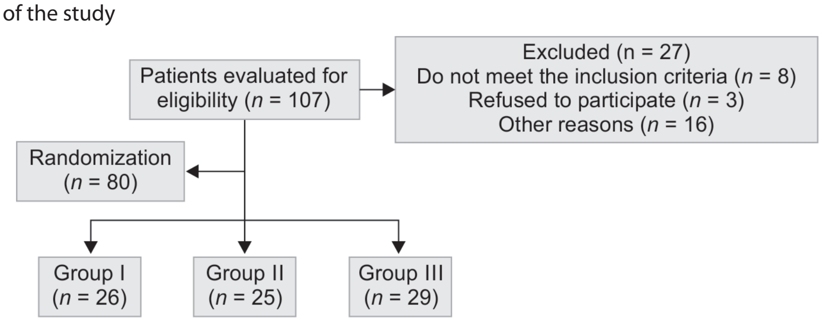


Fig. 3: There was no significant difference in the pain score (VAS) between the groups ($p = 0.49$)

Flowchart 1: Flow diagram of the study



patients.[23] More than 80% of patients undergoing head and neck RT experience an increase in OM as treatment progresses. The OM is one of the main complications of antineoplastic therapy and its clinical manifestations include mucosal atrophy, edema, erythema, ulceration, and intraoral and throat pain and it severely affects oral functions such as taste, swallowing, and speech. The most serious clinical outcomes of OM include impaired quality of life, increased cost and duration of hospital stay, increased incidence of secondary or systemic infections, mortality related to infection, and indirect decrease in survival rate due to possible treatment delays or dose reductions.[16] Thus, attempting to minimize the effects of RT-induced OM, the present study tested three different LLLT protocols by measuring OM in daily degrees for 42 days and observing the role of this therapy in preventing and reducing this condition.

Managing OM is a challenge and many strategies are used to minimize the damage caused by antineoplastic agents,[10] aiming to relieve symptoms during the healing process and reduce the severity of ulcers and even their appearance.[24] In this sense, LLLT has made and continues to make great progress in obtaining recognition from medical authorities, academic journals, the press, popular media, therapists, and other agencies interested in biomedical science.[25] Recent studies[16,26] argue that LLLT is a safe and low-cost therapy that can be used in patients undergoing RT in the head and neck region, with a significant positive impact on the multidisciplinary treatment of HNC. This information agrees with the findings of the present study, in which all 80 patients in the final sample submitted to RT of the head and neck had some degree of OM from the exposure to RT, which was reduced over the 6 weeks of evaluation using LLLT applications.

To review the literature and update the evidence-based for application of PBM for preventing or treating OM, an article was produced, using the PubMed and Web of Science platforms. As a result of the research, the group identified evidence to support clinical practice guidelines for three specific indications: prevention of OM with intraoral PBM therapy in hematopoietic stem cell transplant patients, prevention of OM with intraoral PBM therapy in patients treated with RT without adjuvant CT for HNC, and prevention of OM with intraoral PBM therapy in patients treated with RT and CT for HNC.[15,27] Such statements corroborate the findings of the present study, which found that PBM therapy is effective in preventing and treating OM lesions in HNC patients treated with RT associated or not with CT.

In a randomized controlled trial by Kuhn et al.,[28] a group of children and adolescents undergoing chemotherapy or hematopoietic stem cell transplantation and diagnosed with OM received LLLT intervention with infrared laser (830 nm), with power of 100 mW, and a dose of 4 J/cm^2. Another placebo group underwent sham treatment. On the seventh day after the OM diagnosis, only one out of nine patients in the laser group remained injured, while nine out of 12 patients in the placebo control group still had injuries, demonstrating that LLLT associated to oral care, can optimize OM induced by CT.

The results of the present study also confirm the findings by Marín-Conde et al.,[7] whose research aimed to evaluate the effectiveness of PBM with LLLT as a preventive and therapeutic procedure for the treatment of oral and oropharyngeal OM from radiochemotherapy in patients diagnosed with oral squamous cell carcinoma (OSCC). In their results, the authors show that statistically significant differences between the group that received LLLT and the control group were observed after the fifth week of cancer treatment. While 72.7% of patients in the first group had normal mucosa (OM grade 0), 20% of patients in the control group had OM grade 0, and 40% had OM grade II, which shows that PBM with LLLT reduces the incidence and severity of OM in patients treated with RT and/or CT.

One of the main biological responses evoked by PBM is the relief of pain and inflammation.[29] LLLT inhibits the conduction of C-fibers and increases oxygenation and lymphatic drainage responsible for pain relief after the first minutes of tissue irradiation.[30] In the present study, a 6-week evaluation was also performed on patients previously submitted to head and neck RT receiving LLLT protocols. Although no differences were identified in pain levels of patients, at the end of the evaluation period, only Group III, which associated the application of red and infrared lasers, showed a decrease in sensitivity scores. This occurred considering that positive effects from PBM with multiple wavelengths can be attributed to different levels of absorption because superficial and deep tissues can absorb radiation in different amounts.[31]

According to Bensadoun,[20] for PBM to be effective, irradiation parameters such as the energy supplied, power, frequency, distribution to the appropriate anatomical site, and treatment time must be within the biostimulating dose windows. Noirrit-Esclassan et al.[24] performed extra- and intraoral applications combining two wavelengths (635 and 815 nm) in children undergoing CT and/or RT. These authors found excellent tolerance and symptom relief (gain of two points on the VAS pain scale). As the first symptom of OM described by patients is usually swallowing difficulty due to sore throat, the use of infrared radiation could improve the treatment of these pharyngeal zones because, while the red light (between 600 and 700 nm) penetrates tissues superficially (>2–5-mm deep), infrared radiation (wavelength >700 nm) allows penetration of about 3–4 cm.[24]

Campos et al.[32] performed a study that aimed to compare different phototherapies (LED, high-power laser, and LLLT) for the treatment of CT-induced OM in hamsters through clinical, biochemical, and histological analyses. The authors concluded that LLLT and LED therapies were the best choices for decreasing the severity of OM, accelerating tissue repair, and decreasing the inflammatory process. In the same study, for LLLT, the authors used a laser with a wavelength of 660 nm, 40 mW of power, and energy density of 6 J/cm^2, in five points of application, differing from the present study only regarding power (100 mW) and application points (30 points), according to Figure 1.

When conducting a histological analysis, Lima et al.[31] showed that PBM through double wavelength lasers (830 and 685 nm) at 20 J/cm^2 was superior in fibroblast proliferation and it increased collagen production and organization in a wound model. These results suggest that using two different radiations with different absorptions and penetrations in biological tissues can stimulate the deep and superficial layers of the wound.[31] This result is added to the findings of the present study, where G3 (combined wavelengths) was more effective in reducing the OM score ($p = 0.012$) than the other groups.

Zecha et al.[33] reviewed the action mechanisms of PBM and dosimetric considerations, recommending wavelengths from 633 to 685 nm or 780 to 830 nm, with power between 10 and 150 mW, energy density not higher than 6 J/cm^2 on the surface of the tissue treated, with successive intraoral applications on single points in the mucosa, and administration of two to three times a week or even daily. The three irradiation protocols applied in the present study were within the parameters proposed by Zecha et al.,[33] emphasizing that the protocol associating the wavelengths of 660 and 810 nm was more effective in reducing OM than the protocols using the referred isolated wavelengths.

Despite the variations in instrumentation and dosage parameters, since its introduction in 1967, PBM by LLLT has been improving wound repair and tissue regeneration, affecting different stages of injury resolution.[18] He et al.[16] conducted a study that sought to synthesize the available clinical evidence on the effects of LLLT for preventing and treating CT-induced OM. Hence, 46 elderly HNC patients were randomized into two groups: patients in the laser group received LLLT of 632.8 nm, power of 0.024 W/cm^2, and a dose of 3 J/cm^2 in six anatomical sites bilaterally and five sessions per week, while those in the placebo group did not receive this therapy. As a result, the authors describe reduction of OM and pain in patients of the first group. Likewise, Antunes et al.[26] evaluated LLLT treatment for preventing OM, noting that patients undergoing this therapy were associated with a lower incidence of OM, fewer gastrostomies, and less use of nasogastric tube and opioids.

There are no known adverse side effects of PBM in HNC patients. However, the potential effect on residual and new dysplastic and malignant cells has not been resolved.[18] Brandão et al.[34] performed a retrospective clinical analysis of 152 patients with advanced HNC treated with prophylactic PBM therapy for RT-induced OM. The study results suggested that LLLT can neither promote mutagenesis in tumor cells nor does it seem to increase the risk of recurrent or new primary tumors. The authors noted that PBM appeared to improve the survival of HNC patients treated with CT and attribute this to improving the quality of life that leads to a better response to therapy. There is evidence suggesting that PBM adjuvant to antineoplastic treatment can decrease the interruption rates of the RT and/or CT protocol and consequently contribute to the healing prognosis of patients.[18]

In the present study, the initial sample consisted of 107 adult patients of both sexes undergoing antineoplastic treatment for HNC. However, only 80 completed the full follow-up period, as patients who had clinical complications that prevented the study from taking place were excluded. The limitations of the study that restricted the number of patients per group were: interruption of RT for more than 1 week, difficulty in coordination and/or locomotion that prevented laser application, and poor adherence to the proposed oral hygiene. Even so, the authors believe that the final sample of the groups was representative of the randomization protocols.

Conclusion

From the groups evaluated and the methodology used in the present study, it can be concluded that PBM therapy is effective for preventing and treating OM in HNC patients treated with RT associated or not with CT. The group in which red and infrared lasers were applied in association presented lower OM scores, showing that this combined protocol can offer advantages relative to the groups in which lasers were applied in isolation.

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