Review

The Use of Low-Level Laser Therapy in the Prevention and Treatment of Chemotherapy-Induced Oral Mucositis

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Abstract

The management of oral mucositis is fundamental in maintaining the quality of life of cancer patients as well as the feasibility and effectiveness of non-surgical treatments of cancer. A literature review was carried out in order to update information on the use of low-level laser therapy for prevention and treatment of induced oral mucositis in patients undergoing chemotherapy or conditioning for hematopoietic cell transplantation. Lasertherapy is a simple, non-invasive and atraumatic technique which has shown good results in the prevention of oral mucositis through basic research and controlled clinical trials. Although the precise molecular mechanisms of low-level laser action have not been elucidated, in face of its proven effectiveness in the management of oral mucositis and the absence of side effects, its use should be continued and even encouraged while the results from new studies defining the optimal parameters for laser application are awaited.

Keywords: Mucositis; Cancer Chemotherapy; Low-level laser therapy

Introduction

Chemotherapy is not a specific treatment for cancerous tissue, acting in the growth inhibition of cells that are divided quickly, interfering in cellular division.[1] Thus, as it does not differentiate neoplastic cells, which divide quickly, with that of normal cells that present a high proliferation rate, such as oral mucous or bone marrow cells, this therapy provokes several side effects that are shown in the oral cavity.[1-7]Additionally, the mouth shelters countless bacteria, making the breach of oral mucous integrity possible, allowing the entry of infectious microorganisms in the myelosuppressed host,[1,3,8] which can lead to death. [9,10]

The frequency with which patients undergoing chemotherapy present oral problems is affected by several variables. These can be divided into variables related to the patient and those related to treatment. Factors related to the patient include age, diagnosis, level of oral health before and during the therapy and their systemic condition. The variables related to treatment include the chemotherapeutic agent, frequency dose and the administration of the medication, besides concomitant use of radiotherapy.[11]

The oral complications of cancer chemotherapy are divided into two principal forms in accord with its origin : the problems that result from the direct action of the drug on the oral tissues (direct stomatotoxicity);and the oral problems caused by the modification of other tissues, such as bone marrow (indirect stomatotoxicity).The most common form of direct stomatotoxicity is oral mucositis, a frequent and debilitating effect of chemotherapy.[9,12]

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In spite of being studied for many years, no strategy or standard therapy has been proven effective in the prevention and/or treatment of oral mucositis. Systematic revisions and recent clinical tests have identified potentially effective interventions for the prevention of mucositis; however, the force of evidence that support such interventions varies and the benefits for patients with different types of cancer are still unknown,[12-20] with the unresolved problems of mucositis prevention and treatment still remaining, limiting the efficiency of antineoplastic therapy and adversely effecting the quality of life of patients.[9,21]

The present work aims to present, through a revision of the pertinent literature, current information on the use of the laser under low-level power densities for the prevention and treatment of oral mucositis induced in patients undergoing chemotherapeutic treatment or conditioning for hematopoietic stem cell transplantation (HSCT).

Revision of Literature

Oral Mucositis induced by chemotherapy

It is estimated that the prevalence of oral mucositis varies between 36% to 100% for patients treated with standard high-dose chemotherapy.[12,21,22] Its pathogenesis is tied to the reduced cellular renovation induced by chemotherapy in the basic layers of the epithelium, which becomes incapable of reaching the appropriate renovation of desquamated cells.[1] Cells that are divided more slowly and cell senescence are less sensitive to chemotherapy action than those cells of the oropharynge, intestinal epithelium and bone marrow that are divided quickly. Oral mucosa is especially vulnerable because of being composed of membranes that have a high mitotic rate of cellular renovation and epithelial maturation.[4,23]

Clinically, oral mucositis presents with inflammation of the mucosa of the oral cavity, which varies in redness and ulceration severity.[9,10,21]After initial erythema, the development of white desquamated plaques follows. Epithelial crust and fibrinous exudate lead to the formation of a pseudomembrane.[24,25] The most severe form of mucositis is represented by ulceration of the epithelium and exhibition of the richly innervated underlying stromal connective tissue,[22] generally occurring between five to seven days after drug administration.[8]

The lesions mainly affect the nonkeratinized oral mucosa, involving principally the region of the soft palate, buccal mucosa,[1,8,22,26] lateral border of the tongue, pharyngeal wall, tonsillar pillars 1, lips, anterior two-thirds of the tongue and mouth floor.[8,22,26]

Besides altering mucosal integrity, chemotherapy also alters the microbial flora that normally is present in the oral cavity, the quantity and composition of saliva, and epithelial maturation.[23] The resultant compromised mucous barrier represents a risk factor for morbidity in oncologic patients and mortality in myelosuppressed[4] patients, serving as an entry point for the spread of bacterial, fungal and viral infections.[2,7,27,28] Secondary infections may lead to severe systemic infections.[2,3,6,7,14,22,26-33]

The patients invariably present symptoms of pain[9,12,22,24] with the incapacity of ingesting foods or liquids,[21,24,34] consequently leading to malnutrition[34] and to the necessity of parenteral administration of narcotics for palliative relief and the prolongation of the hospital stay.[24]

All of these conditions can limit the capacity of the patient to tolerate chemotherapy in a way that can delay or alter the therapeutic scheme, compromising its efficiency in the treatment of cancer.[1,21] They can make subsequent treatments impossible or elevate the cost, putting the survival of the patient in risk or irreparably altering the quality of life of the patient and their families.[2,5,14,26,29,30,32,35,36] Thus, it is important that mucositis is prevented whenever possible or at least treated to reduce its gravity and avoid associated complications.[21]

In spite of being one of the most investigated subjects among supportive care in cancer,[37]no strategy or standard therapy has proven effective in its prevention and/or treatment.[12,20] However, systematic revisions and recent clinical tests have identified the use of the low-level laser as a potentially effective intervention for the prevention and treatment of mucositis.[9,16,17,20,26,32,34-36,38-43]

Laser Therapy

The word laser is an acronym for light amplification by stimulated emission of radiation. The non-ionizing electromagnetic radiation emitted is a light source with distinctive characteristics. The laser is a type of light in which photons are identical and, thus, are emitted according to identical trajectories, direction, sense, amplitude and phase. Therefore, they are devices able to emit light with a single and definite wavelength.

The optical radiation produced by several types of lasers are similar, since they are generated through the same principal; however, it is possible to work with the

laser looking for relatively specific clinical results, hence, what determines its interaction with tissue is the density of optical power of the system and its wavelength.[25,44] Under low-level power densities, the laser presents a modulating effect on the cells, while presenting an inhibiting effect in high-level power densities.[12]

When the laser is offered in a low-level density, but sufficiently high so that it uses the cell target in a way of stimulating its membrane or organelles, inducing biomodulation, in other words, the tissue will try to restore the state of normality of the region affected.[44]

Because of being a non-invasive, simple and atraumatic technique without clinical reports of toxicity,[25]the application of light is ideal for the treatment of tissues without risk of damaging healthy cells through invasive procedures.[45]

Interaction Between the Laser and Tissues

Therapy with low-level laser, or laser therapy, has been investigated in several areas of medicine.[37]

Laser therapy corresponds to the local application of a high photon density monochromatic light source.[21] The effects of this intervention have been confirmed by numerous in vitro studies.[25] Its effects are clinically shown through trophic - regenerative, anti-inflammatory and analgesic actions.[12,21,25,26,43,44]

The precise mechanisms of the laser that promote healing and reduction of inflammation and pain at the cellular and molecular level are still not completely elucidated, but some hypotheses have been suggested. According to Karu,[46] the energy of the laser is absorbed in the mitochondria by cytochromes, provoking the transmission of electrons and leading to an increase of protein synthesis and activation of the production of energy (ATP), promoting the cicatricial effect.

Arora et al.[12] suggests the stimulation of quick epithelization and proliferation of fibroblasts (collagen) by laser photons (in the red wavelength) in human and animal tissue cultures. Biron et al.[9] included increased cellular division and miofibroblast synthesis.

Jaguar et al.[20] attributed the potential of the laser for the improvement in healing and pain relief to the increase of cellular division and alteration of nerve conduction through the liberation of endorphins and encephalins.

Due to the increase of vascularity and re-epithelization of lesion tissue,[21] the laser has been recommended to stimulate the healing of difficult healing ulcers,[12] such as oral mucositis induced by anti-neoplastic therapies.

Laser Therapy in the Prevention and Treatment of Oral Mucositis

In spite that the action mechanism of laser therapy in mucositis pathobiology remains unknown,[37]several authors have suggested its preventive[8,9,12,21,32,41,42,47,48] as much as its curative use.[12,20,21,35,36,48,49]

Six clinical studies were found in the literature addressing the use of laser therapy in the reduction of mucositis pain induced by chemotherapy and induction in TCH regimes for patients with cancer. [20,34,36,41-43] Data on study design and the parameters used in laser therapy can be seen in the Table 1.

Cowen et al.,[41] in a randomized multicentric study published in 1997, pointed to the efficiency of the low-level laser in the prevention of oral mucositis induced by chemotherapy for the conditioning of cells for hematopoietic stem cell transplantation, reducing the severity of oral mucositis in treated patients.

In this study, the laser was administered to the intervention group during five days of conditioning up to the day of transplant. The patients of the intervention group presented 33% reduction of oral mucositis grades III and IV in relation to the control group. Additionally, there was a statistically significant reduction in the time of oral pain in patients who had undergone laser therapy, where the average time of pain was 20.3 days for the patients of the control group and 12.7 days for the patients of the intervention group, suggesting clinical action of laser therapy in the prevention of subjective symptoms associated to oral mucositis. The authors point out the continued necessity of new studies to determine the ideal moment for laser application to maximize the reduction, or preferably, to prevent mucositis.[41]

In a study conducted by Nes and Posso,[36]the authors concluded that the low-level laser, in the parameters used in their work, had an analgesic effect immediately after its application in patients with mucositis oral induced by cancer chemotherapy.

Jaguar et al.[20] also investigated the clinical effects of laser therapy in the prevention and reduction of oral mucositis induced in patients who had undergone hematopoietic stem cell transplantation. In this study, an experimental group (n=24) was compared with a historical control (n=25) in the archive system of Hospital A.C. Camargo, Sao Paulo, Brazil.

The results of the work are in agreement with the findings of Cowen et al.,[41] presenting a reduction of the average time of pain for the intervention group (2.45 days) in relation to the control group (5.64 days) (p =

Table 1 - Distribution of the clinical studies addressing laser therapy for the prevention of oral mucositis in patients who have undergone anti-neoplastic therapy according to study type, type of oncologic treatment, laser therapy parameters and evaluation form.

				Lase Therapy Parameters			Evaluation	
Reference	**Study Type**	**N(Study/ (control)**	**Anti-neoplastic Therapy**	**Wave-length**	**Potencial (mW)**	**Dose (J/cm²)**	**applic. mode**	**Scale used**	**Frequency**
Cowen et al., 1997	RCT*	15/15	High-dose	632.8	60	1.5	5 days	Scale of Walsh et al	Daily for 20 days
Nes, Posso, 2005	Case series	13/0	Chemotherapy		250	35	5 days	Método de Brown e VAS***	Twice/ day for 5 days
Jaguar et al., 2007	Case series	24/25 (historic)	Chemotherapy	830	10	2.5	5 days	WHO**	Not specified
Cruz et al., 2007	RCS*	29/31	TCH		60	4	5 days	WHO**	Weekly for 3 weeks
Antunes et al., 2007	RCS*	19/19	Chemotherapy + TCH	660	50	4	7 days	OMAS***+ WHO**	7 days
Antunes et al., 2008	Case series	11/0	TCH	780	50	8	6 days in avg.	OMAS*** + WHO**	Not specified

*RCT: Randomized Clinical Trial; **WHO: World Health Organization scale; *** OMAS: oral mucositis evaluation scale; **** VAS: Visual Analogue Scale

0.04). Accordingly, laser therapy promoted pain relief, reduced the severity of oral mucositis and diminished the necessity of administration of morphine to patients.[20]

Jaguar et al.[20] argued that severe oral mucositis in patients who had not undergone laser therapy took more time to heal, affecting significantly the quality of life. This occurs due to the neutropenic condition of patients who, after presenting oral mucositis, are predisposed to bacteremia, fungemia and septicemia.

Additionally, the increase of one point in the scale of oral mucositis was associated with a significant increase in oral pain. According to the authors, from the perspective of the patient, acute oral pain is the most debilitating effect of mucositis because it interferes in the capacity of eating, swallowing and speaking, and results in an increase in the number of days of morphine and parenteral nutrition administration.[20]

Cruz et al.[34] evaluated the role of low-level laser in the prevention of mucositis induced by chemotherapy in children and adolescents with cancer.

Contradicting previous studies, the evaluations carried out on days 8 to 15 showed prevalence of oral mucositis almost identical in the two groups, with a tendency for mucositis in an elevated degree on day 8 in the laser group. The authors did not find any evidence of benefit of the preventive use of low-level laser in patients with cancer undergoing chemotherapy with good oral hygiene. Cruz et al. [34] suggested that these results might go against the results of previous studies carried out in adults due to a three time larger rate of proliferation of basal cells in children, which might help younger patients cure their injuries more quickly. The authors pointed still to the possibility of a protective effect of the rigorous oral hygiene carried out in all the volunteers previous and during study participation.

In a clinical test conducted by Antunes et al.,[42] the clinical effects of laser therapy were again investigated in the prevention and reduction of the severity of oral mucositis induced in patients who had undergone TCH conditioning. In this study, the application of the laser was initiated on the first day of conditioning (D-7) and stopped on the day of neutrophila recuperation. In spite of a delay in the onset of mucositis in the patients of the intervention group, there was no statistically significant difference noted between the groups. Also, there was no statistical difference observed between the groups on total time with mucositis. However, in the laser group , 94.7% of the patients presented oral mucositis with a grade inferior or equal to grade II, including 63.2 % with grade 0 and I, whereas, in the control group, only 31.5 % of the patients presented oral mucositis with a grade inferior or equal to grade II ($p < 0.001$). Calculating the total ulcerated area, 5.3% of the laser group presented ulcers of 9.1 cm^2 to 18 cm^2, whereas 73.6% of the control group presented ulcers of 9.1 cm^2 to 18 cm^2 ($p < 0.003$).

Antunes et al.[43] evaluated the clinical effects of

laser therapy in the reduction of oral mucositis severity induced in 11 patients undergoing TCH conditioning. Although the sample of the work had been reduced, the authors concluded that laser therapy is efficient in the treatment of oral mucositis, because, even in patients with grade IV mucositis, the time of ulcer healing was an average of 6 days and the patients did not mention any uncomfortable sensation while the laser was applied. These results indicated that the use of laser therapy in patients undergoing TCH conditioning is a powerful instrument in the treatment of induced oral mucositis and is now a standard treatment procedure in this group of patients in their hospital.

Laser therapy is a simple technique, atraumatic, and useful in the treatment of mucositis of various origins [25]. It has been reported that its use can reduce the incidence of oral mucositis,[47] delaying onset,[9,32] diminish progression,[35] reduce severity peak,[9,32,34,47] accelerate process repair ,[9,32,35,49] significantly reduce the pain of previous mucous lesions [8,34,35,49] and avoid the incident of new lesions in the same site;[9] in addition to being useful in the cure of oral mucositis.[12]

The specific cellular mechanisms affected by laser therapy are still not elucidated, thus, the realization of more basic research in this area is necessary,[12,35,41] since fundamental action mechanisms can be found and can have potential importance in the management of oral mucositis and other morbid conditions.[35] It is worth emphasizing that in 1997, Hashieh et al. [48] demonstrated that laser therapy is not a cytotoxic treatment. In spite of laser irradiation not provoking any significant clinical side effects, this was the first study to demonstrate the absence of side effects at the cellular level.

The results of clinical research addressing the use of laser therapy in the handling of oral mucositis have been positive. However, the parameters used have been exceedingly varied (Table 1). In this way, to better understand laser therapy, the realization of more prospective randomized controlled studies is necessary to confirm its effect on oral mucositis [8,12,20,21,35,37,42] and to define the parameters and ideal protocols of laser application.[25,37] Also, the realization of additional studies involving the quality of life of patients and laser therapy cost-efficiency analysis is important.[42]

At present there are studies presenting promising results in the prevention of oral mucositis and in the reduction of pain associated with children who had undergone bone marrow transplant using noncoherent sources of light.[45]

Conclusion

The handling of oral mucositis is an aspect of fundamental importance in the maintenance of the quality of life of the oncologic patient as well as in the viability and efficiency of non-surgical treatments of cancer. Although the precise mechanisms of the low-level laser that promote healing and reduction of inflammation and pain have still not been elucidated, in front of the proved efficiency of laser therapy in its handling and absence of side effects, at the clinical or cellular levels, its use should be continued and even encouraged while waiting for the results of new studies that will define the ideal parameters of application for obtaining the best results.

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