Laser Phototherapy as Topical Prophylaxis Against Head and Neck Cancer Radiotherapy-Induced Oral Mucositis: Comparison Between Low and High/Low Power Lasers

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Background and Objective: Oral mucositis is a dose-limiting and painful side effect of radiotherapy (RT) and/or chemotherapy in cancer patients. The purpose of the present study was to analyze the effect of different protocols of laser phototherapy (LPT) on the grade of mucositis and degree of pain in patients under RT.

Patients and Methods: Thirty-nine patients were divided into three groups: G1, where the irradiations were done three times a week using low power laser; G2, where combined high and low power lasers were used three time a week; and G3, where patients received low power laser irradiation once a week. The low power LPT was done using an InGaAlP laser (660 nm/40 mW/6 J cm^{-2}/0.24 J per point). In the combined protocol, the high power LPT was done using a GaAlAs laser (808 nm, 1 W/cm^2). Oral mucositis was assessed at each LPT session in accordance to the oral-mucositis scale of the National Institute of the Cancer—Common Toxicity criteria (NIC-CTC). The patient self-assessed pain was measured by means of the visual analogue scale.

Results: All protocols of LPT led to the maintenance of oral mucositis scores in the same levels until the last RT session. Moreover, LPT three times a week also maintained the pain levels. However, the patients submitted to the once a week LPT had significant pain increase; and the association of low/high LPT led to increased healing time.

Conclusions: These findings are desired when dealing with oncologic patients under RT avoiding unplanned radiation treatment breaks and additional hospital costs. Lasers Surg. Med. 41:264–270, 2009. © 2009 Wiley-Liss, Inc.

Key words: analgesia; head and neck radiotherapy; oral pain; oncology; wound healing

INTRODUCTION

Oral mucositis is a dose-limiting and painful side effect of radiation and/or chemotherapy in cancer patients. It occurs in almost all patients undergoing radiotherapy (RT) for treatment of head and neck cancers and in the majority of patients receiving conditioning regimens for hematopoietic stem cell transplantation (HSCT) [1,2]. In addition, between 20% and 60% of patients undergoing treatment for other types of cancer experience significant mucositis [1]. Moreover, ulcerative mucositis is the major limitation to continuous, uninterrupted RT and concurrent chemoradiotherapy (CRT) in the management of head and neck cancer [3].

Unplanned radiation treatment breaks resulting from ulcerative mucositis and the associated acute side effects negatively impact treatment outcomes for many types of tumors, but the detrimental effect appears greatest in head and neck cancer [4]. Thus, oral mucositis is associated with increased morbidity and mortality in addition to significant additional hospital costs [5,6].

Onset of oral mucositis is a biologically complex process that has been partially elucidated at the molecular level [1,7–9]. Radiation and chemotherapy lead to the generation of reactive oxygen species (ROS), which in turn activate several signaling pathways in the submucosa and epithelium [9]. Among these, nuclear factor-B is thought to be important as it mediates the release of cytokines and

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cytokine mediators, cell adhesion molecules, acute-phase proteins, and stress response genes. This, in turn, leads to loss of epithelial cell renewal, apoptosis, atrophy, and ulcer formation. Amplification of these events can also occur through the subsequent infection of compromised mucosal barrier by oral bacteria [7].

Strategies for reducing oral mucositis in order to address this serious impediment to cure have been proven to be inadequate, leaving a very important unmet medical need [3]. The treatments for oral mucositis includes: administration of topical antimicrobial agents [10], vitamins [11,12], growth factors [13,14], mouth washes [15], and cryotherapy [16,17].

The continued investigation of new therapies to attenuate oral mucositis for improving both the tolerability and efficacy of RT in head and neck cancer introduced the laser phototherapy (LPT) [10,18–24].

Studies have shown that LPT can reduce the severity of oral mucositis and pain [20,21,23,24]. The effect produced by LPT is based on the capacity to modulate various metabolic processes, by conversion of the laser light energy input through biochemical and photophysical processes, which transform the laser light into energy useful to the cell. Visible laser is absorbed by chromophores in the respiratory chain of the mitochondria, with increase in ATP production that results in increased cellular proliferation and protein synthesis, aiding tissue repair [25]. For analgesia, it has been shown that peripheral nerve stimulation by laser alters hyperpolarization of the cellular membrane and increases the concentration of ATP, which could contribute to maintaining the stability of the membrane and increase the pain threshold [26]. Moreover, LPT can enhance peripheral endogenous opioid production [27] and decrease serum prostaglandin E_2 [28]. In addition to these benefits, LPT is shown to be a simple and atraumatic technique in the treatment of oral mucositis and is well tolerated by patients.

Our research group has been studying the effects of LPT on oral mucositis mostly induced by chemotherapy or CRT conditioning for HSCT [20,24]. The visible red wavelength reduced the severity of oral mucositis and pain scores [20]. Moreover, LPT is able to keep mucositis levels at grades I and II [24]. However, the studies of prophylaxis of RT-induced oral mucositis by LPT are scarce. Thus, clinical trials are necessary to test the effectiveness of LPT in patients undergoing RT.

LPT can be continuous applied in daily protocols on patients admitted in hospitals with positive effects [24]; however, in patients under ambulatory attendance, daily treatment may be difficult due economic problems as well as to the debilitated physical conditions. For these patients a fractioned laser application would be more feasible; however, the effect of this non-continuous LPT on the reparation and analgesia in RT-induced mucositis is not known. Thus, the aim of the present study is to analyze the effect of different frequencies (one and three times a week) and laser application protocols (high and/or low power) on the grade of mucositis and degree of pain in patients under RT.

PATIENTS AND METHODS

Patients

A prospective study was conducted at Special Laboratory of Laser in Dentistry (Laboratório Especial de Laser em Odontologia—LELO), from November 2005 to March 2008. Thirty-nine patients with head and neck cancer under RT treatment participated in this study. The patients were referred to LELO from the "Instituto do Cancer Arnaldo Vieira de Carvalho (IAVC—Santa Casa)."

Ethical Considerations

The protocols for this study were approved by the Ethics Committee of the Faculdade de Odontologia at the Universidade de São Paulo, Brazil, and written informed consent was obtained from all patients. The care with the patients throughout the study was conducted in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2000.

Clinical Procedures

During clinical examination the medical history of the patient was recorded. Data related to base illness, type and stage of RT treatment, association or not to chemotherapy were collected during the whole treatment.

After clinical examination, the patients received a kit containing toothbrush, dentifrice, mouth wash and artificial saliva (Biotene® kit, Laclede do Brasil, SP, Brazil) and subsequent oral hygiene instructions.

Three different laser phototherapeutic protocols were used. Independently of the protocol used, oral examinations were done at the ambulatory at each irradiation session and the degree of mucositis and pain were recorded.

Laser Phototherapeutic Trials

Three laser phototherapeutic protocols were used. Two dentists were trained for conducting the laser irradiations in a standardized manner. For randomized patients two protocols with only low power laser were used. For patients exhibiting oral mucositis with ulcers at the first visit a protocol combining low and high power lasers (both in low intensity range) was done. The irradiations were done three times a week using low power laser (G1, $n = 16$) or combined high and low power lasers (G2, $n = 9$) and once a week using low power laser ($G3 = 14$).

The therapeutic protocols were initiated at the first visit (within 21 days after the first RT session) and ended when any signs of oral mucositis became extinct. The time for complete mucosal healing was recorded.

Phototherapy With Low Power Laser

For the low power phototherapy, an InGaAlP diode laser (Twin Laser—MMOptics® Ltda, São Carlos, SP, Brazil) with a wavelength of 660 nm was used, according to Campos et al. [23] and Eduardo et al. [24]. The irradiation mode was punctual and in contact, perpendicular to the oral mucosa. The power used was 40 mW, energy density of 6 J/cm^2 and energy per point of 0.24 J [23,24]. Irradiation time was 6 seconds per point based on the laser beam spot size of 0.036 cm^2. The irradiations were done intra-orally avoiding the tumor site, as follows: 12 points in each buccal mucosa (right and left), 8 in the superior and inferior labial mucosa, 12 in the hard palate and 4 in the soft palate, 12 on the lingual dorsum, 6 on the lateral edge of the tongue bilaterally, 2 on the right and left pillar of the tongue, 4 on the floor of the mouth and 1 in the labial comissure bilaterally.

Phototherapy With Combined Low/High Power Lasers

In the combined protocol, the high power LPT was followed by the low power LPT, as described above.

The high power LPT was done using a GaAlAs high power diode laser (Soft Lase, Zap Laser Ltd, Pleasant Hill, CA) with a wavelength of 808 nm, following the protocol of Campos et al. [23]. This therapy was only used in patients presenting ulcers at the first visit. The irradiation was restricted to the ulcerate sites. Laser light was delivered through a 400 μm contact optical fiber. The power output at the display was set at 1.0 W and the laser was applied in continuous-wave mode (power density of 1 W/cm^2). The irradiations were done manually and perpendicular to the oral mucosa surface in a defocused mode at a distance of 1 cm from the lesion. Each cm^2 of the lesions was irradiated during 10 seconds with scanning movements (5 seconds with vertically movements and 5 seconds with horizontally movements) and energy density of approximately 10 J/cm^2.

For all therapeutic protocols, before and after each session, power output was checked using a power meter (Coherent Molectron®, Santa Clara, CA). The laser irradiations were done following biosafety rules.

Mucositis Assessment

Oral mucositis was assessed in the first visit and at each LPT session before the laser irradiations. Two dentists were trained for performing standardized mucositis assessment in accordance to the National Institute of the Cancer—Common Toxicity criteria (NIC-CTC) RT-induced oral mucositis scale, as follows [1]:

(0) patients with oral mucosa presenting no visible alteration;
(1) presence of erythema;
(2) ulcers with up to 1.5 cm diameter and non-contiguous;
(3) ulcers larger than 1.5 cm diameter and contiguous;
(4) ulcers exhibiting necrosis and bleeding;
(5) death related to toxicity.

Pain Assessment

The patient self-assessed pain was measured by means of the visual analogue scale (VAS) [29], which quantifies pain from 0 to 10, in an ascending order. This assessment was made before each LPT session.

Statistical Analysis

Clinical data related to age and RT dosage were compared by one-way ANOVA, whereas gender, association or not to chemotherapy and number of laser irradiations were compared by Kruskal–Wallis complemented by the Dunn's test. The initial scores of mucositis and pain and those recorded immediately after the last RT session were compared by Wilcoxon Signed Ranks. The time required for the total remission of the oral mucositis after the last RT session was compared by Kruskal–Wallis complemented by the Dunn's test. Correlations between grades of mucositis and pain were assessed by the Spearman's coefficient test. The level of significance adopted was 5% ($P \leq 0.05$).

RESULTS

A total of 39 patients were included in this study. Laser irradiations were well tolerated with no detectable adverse side effects. Clinical data of the patients are presented in Table 1. The patients ranged from 15-year-old in the G2 to 79-year-old in the G1. The patients received RT dosage (in Gy) varying from 50 in G2 and G3 to 70.4 in G2. There were no significant differences amongst the different experimental groups in relation to age, gender, RT doses and association or not to chemotherapy ($P = 0.53$, 0.06, 0.24, 0.12, respectively). The patients of G1 and G2 received similar number of laser irradiations that were significantly smaller in the G3 ($P = 0.0001$).

There were no differences between the grades of mucositis in function of LPT protocols. Independently of the LPT protocol employed the grade of mucositis at the time of the last RT session was similar to that recorded at the first LPT session (Fig. 1).

The patient self-assessed pain showed a significant increase ($P = 0.011$) from the beginning of the LPT and the last RT session in the group that received the low power LPT just once a week (G3). The other two groups presented similar degree of pain that were maintained in the same levels from the beginning of the LPT to the end of the RT (Fig. 2).

All patients finished the LPT sessions with neither oral signs of mucositis nor pain. The time required for the total remission of the oral mucositis after the last RT session was different in function of the LPT protocol adopted. The clinical signs of the oral mucositis in patients of G2, where the combined high/low power lasers were used, took significantly more time ($P = 0.04$) to heal than those of the other groups. In both protocols of solely low power LPT the oral mucositis healed in similar time (Fig. 3).

There was a strong positive correlation between the grades of mucositis and the degree of pain ($rs = 0.62$, $P < 0.0001$) for patients of all LPT protocols.

TABLE 1. Clinical Characteristics of the Patients

	G1 (n = 16)	G2 (n = 9)	G3 (n = 14)
Age (years)	57.63	50.67	54.92
Female gender	56.25%	44.00%	14.3%
Surgery	69.00%	89.00%	93.00%
Chemotherapy	69.00%	56.00%	14.30%
Laser irradiations	13[a]	12[a]	5[b]
Total RT dose (Gy)	65	61	62

Different letters means statistically significant difference among the groups.

DISCUSSION

LPT using three different protocols was applied to 39 patients for treating or preventing oral mucositis. These patients were under RT for head and neck cancer associated or not to chemotherapy. The LPT protocols involved either low power laser once or three times a week or association of high/low power lasers three times a week. All protocols of LPT led to the maintenance of oral mucositis scores in the same levels until the last RT session. Moreover, LPT three times per week was better than one and the combination of low power laser with high power laser is more effective for pain relief but prolongs healing time.

The improved pain relief may very well be a low price for another week of therapy. Moreover, for improving the patient's quality of life, the most significant effect of LPT is the control of pain observed when high power laser was used. In addition, it is important to highlight that besides avoiding the antineoplasic treatment break, the pain relief also results in essential improvements of basic oral functions, such as drinking, eating, swallowing, and speech. On the other hand, the prolongation of healing time, observed in the combined LPT group, possibly resultant of an inhibitory effect of cicatricial events favoring the pain relief, may perhaps be a problem. In fact, the maintenance of unhealed lesions increases the possibility of secondary infection occurrence. Although this healing time was higher than those observed in both groups of low power laser treatment, this healing time was smaller than that of non-laser treated lesions, as observed in the literature [2].

The efficacy of LPT in the head and neck cancer RT-induced mucositis was similar to that previously observed in patients under chemotherapy or CRT conditioning for hematopoietic cell transplantation [24]. Our results are in accordance with studies in the literature that show the efficacy of LPT in reducing the grade of mucositis in those patients with grade III or IV, and for maintaining patients at grades I and II [19,24,30]. The maintenance of mucositis scale by LPT during the RT observed in our study is of importance, once without LPT the patients have the tendency to develop more intense oral mucositis and pain during the course of the RT [2,31,32].

The patients referred to LELO were under ambulatory attendance and received fractioned laser irradiation. It is known that fractioned LPT can lead to more detectible effects than one-time irradiation [33]. In fact, the three times a week LPT protocols, independently of using

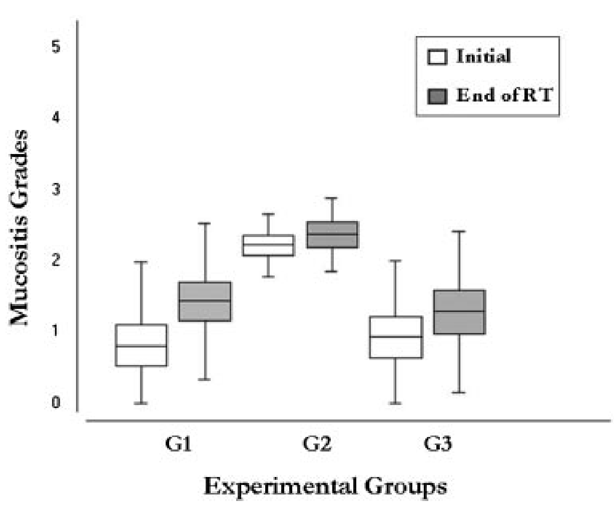

Fig. 1. Mean and standard deviation of initial and final mucositis grade for all experimental groups (G1, G2, and G3).

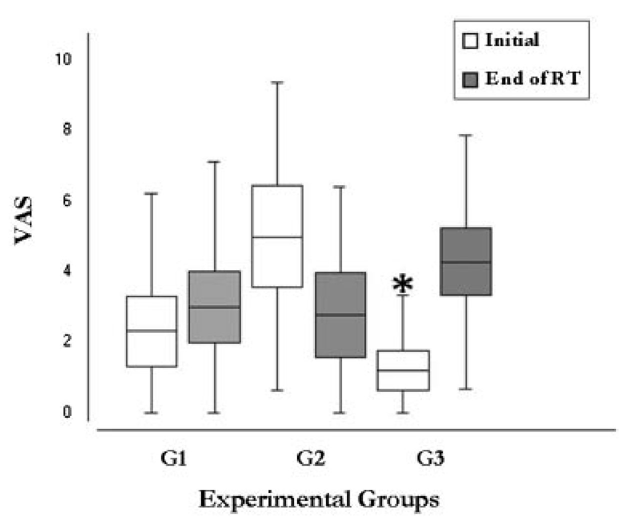

Fig. 2. Mean and standard deviation of initial and final VAS scores for all experimental groups (G1, G2, and G3). * Means statistically significant difference between initial and final VAS score into the same group (G3).

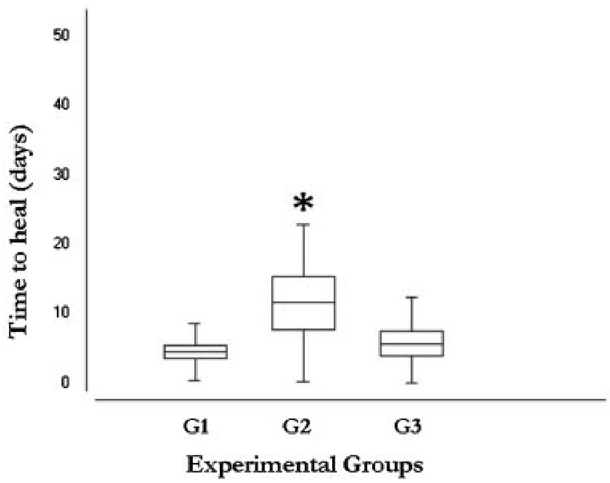

Fig. 3. Mean and standard deviation of the time (days) of complete healing of oral mucositis. *Means statistically significant difference among the groups.

only low power laser or the association between low and high power lasers, were the treatments that reached the desired effects (e.g., maintenance of mucositis scores and pain). As observed in our patients and in the literature [32] there is a positive correlation between oral mucositis scores and pain. Thus, even with increased healing time in the group treated with the association high/low power lasers, the maintenance of oral mucositis scale prevented pain increase; which ultimately improved the quality of life of such patients.

Radiation-induced mucositis stays at peak for at least 2 weeks following the completion of RT (typically 60–70 Gy). As a result, it is not uncommon for patients receiving head and neck RT to have severe mucositis persisting for 5–7 weeks [2]. Our results showed that patients under LPT using only low power laser reached total healing of oral mucositis within 1 week after the end of RT. Although, patients who received the association of low and high power lasers needed more time (approximately 2 weeks) to accomplish mucositis healing, their pain was controlled and exhibited a tendency to decrease. In fact, immediately after the LPT session in this group, the patients reported complete absence of pain. This feature could be resultant of some interaction between the light and the peripheral nervous system, through some membrane cell depolarization, blocking the nervous impulse. This could be true, once Chow et al. [34] have shown that infrared laser is able to block fast axonal flow, providing a mechanism for a neural basis of laser-induced pain relief.

Based on the results of our study as well as others, the advantages of using LPT in patients undergoing antineoplasic treatment for controlling signs and symptoms of oral mucositis are clear [18,21–23,35,36]. However, the mechanisms underlying the effects of LPT in these patients are still not totally known. Our research group has shown in vitro and in vivo, that LPT can act on cell proliferation, cytokines production, as well as in mast cell degranulation [37–39]. These are physiological steps related to inflammation and wound healing processes, which in turn could participate in the positive effects of LPT in the patients under RT.

It is important to highlight that the use of LPT in patients under antineoplasic treatment has beneficial effects by modulating mucositis phases, decreasing the time of healing and for pain relief [20,21,23,24]. Besides that, the association of low power lasers with photosensitizers, the so called photoactivated disinfection (PAD), can also be used for reducing microbial contamination of periodontal pockets or infected ulcerative lesions of these patients [23]. These features, associated to the fact that LPT is an atraumatic and non-invasive technique, explain why the use of laser in the oral cavity of oncologic patient is increasing.

It is known that the laser irradiation parameters, as well as the frequency of applications are key factors in order to reach the desired effects of LPT in each clinical situation. In patients under RT for treating head and neck cancers, we could show a beneficial effect of a fractioned therapy (three times a week) using low power laser alone or associated to high power laser. However, new studies must be done for searching more accurate parameters nor only for controlling the oral mucositis as reported here, but also for fully avoiding the undesired side effects of radio as well as chemotherapy.

CONCLUSIONS

LPT using low power laser alone or associated with high power laser when applied three times a week maintains the oral mucositis grades in levels I and II. Moreover, this fractioned LPT also prevents pain increase. These findings are desired when dealing with oncologic patients under RT avoiding unplanned radiation treatment breaks in addition to significant additional hospital costs.

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