Photomedicine and Laser Surgery
Volume 31, Number 12, 2013

Pp. 613–618
DOI: 10.1089/pho.2012.3327

Low-Level Laser in Prevention and Treatment of Oral Mucositis in Pediatric Patients with Acute Lymphoblastic Leukemia

Jurema Freire Lisboa de Castro, DDS, MSc, PhD,[1] Elizabeth Galamba Fernandes Abreu, DDS, MSc,[1] Andreza Veruska Lira Correia, DDS, MSc,[1] Catarina da Mota Vasconcelos Brasil, DDS, MSc,[1] Danyel Elias da Cruz Perez, DDS, MSc, PhD,[1] and Francisco de Paula Ramos Pedrosa, MD[2]

Abstract

Objective: The aim of this study was to evaluate the influence of low-level laser therapy (LLLT) on the prevention and treatment of oral mucositis (OM) in pediatric cancer patients taking methotrexate. ***Background data:*** OM is a very common, potentially severe side effect, caused by treatment with radiotherapy and chemotherapy for cancer. ***Methods:*** Forty patients with acute lymphoblastic leukemia, who received high doses of methotrexate, were distributed into two groups. Group A (Preventive Group) was composed of patients who received preventive laser (red-subgroup A1 or infrared-subgroup A2) for 5 days, beginning on the 1st day of infusion. Group B (Treatment Group) was composed of patients who received laser treatment only if they developed post-chemotherapy mucositis (red-subgroup B1 or infrared-subgroup B2). Laser was used at wavelengths of 660 or 830 nm with output 100 mW, power density 3.57 W/cm^2, spot size 0.028 cm^2, energy of 1 J, resulting in an energy density of 35 J/cm^2 for 10 sec in the prophylactic group, and energy of 2 J, resulting in energy density of 70 J/cm^2 for 20 sec in the therapeutic group. ***Results:*** The percentage of patients who did not develop OM was higher in Group A (60% vs. 25%). In Group B, 3/20 patients developed grade IV OM (15%), and a significant difference was found between the two subgroups at the end of treatment ($p = 0.019$). ***Conclusions:*** Prophylactic laser produced a better outcome than when patients did not receive any preventive intervention, and red laser (660 nm) was better than infrared (830 nm) in the prevention and treatment of OM.

Introduction

Oral mucositis (OM) is a very common, potentially severe side effect, caused by treatment with radiotherapy and chemotherapy (CT) for cancer. It can be a limiting factor in the scheduled cancer treatment regimen, leading to suspension or interruption of the programmed treatment, with the consequent decrease in its effectiveness and even in the patient's survival.[1]

Patients with OM often experience intense pain, leading to difficulty with eating and speech. In addition, mucosal barrier injury represents a portal of entry for opportunistic infections.[2,3]

The pathophysiology of mucositis is dynamic and multifactorial, which includes five phases: initiation, upregulation and message generation, signal amplification, ulceration, and healing.[4]

The initiation phase is followed by both DNA and non-DNA damage. Direct cellular injury targeting the basal epithelial cells occurs simultaneously with the generation of reactive oxygen species (ROS). In the primary damage response (message generation phase) a series of transcription factors are activated and the production of pro-inflammatory cytokines such as nuclear factor-κB (NF-κB), tumor necrosis factor-alpha (TNF-α), interleukin-1, (IL-1), and interleukin-6, (IL-6), nitric oxide (NO), ceramide, and matrix metalloproteinases (MMPs) occurs, which leads to apoptosis and tissue injury. The inflammatory modulators are activated, and provide a positive feedback loop (signal amplification) that drives the destructive process, so that the oral epithelium eventually breaks down and ulcerates (ulceration phase). The healing phase is also biologically dynamic, with signaling from the submucosal extracellular matrix stimulating the migration, differentiation, and proliferation of epithelial healing.[4–7]

These biological events are influenced by various factors, such as drug toxicity, dose, the interval between cycles,

[1]Postgraduate Program in Dentistry, Oral Pathology Unit, Federal University of Pernambuco, Recife, Pernambuco, Brazil.
[2]Pediatric Oncology Department, Professor Fernando Figueira Integrated Medical Institute, Recife, Pernambuco, Brazil.

associated radiotherapy, the general health of the patient, susceptibility to the CT agents, and patient's dental condition and oral hygiene.[2]

Many treatments and strategies have been described to prevent and reduce the severity of mucositis, such as an intensive oral care protocol, antimicrobial agents, anti-inflammatory agents, cytoprotective agents, growth factors, natural and homeopathic agents, and local anesthetics.[1,8] Clinical trials on these modalities have yielded inconsistent results; therefore, none of them have become a gold standard adjunct with proven efficacy.

Because of the ease of use, absence of side effects, low cost of the equipment, and positive results, the use of LLLT has been shown to be a new therapeutic option that can be used for management of OM.[9,10] Therefore, this study described the effect of LLLT on the prevention and treatment of OM in pediatric patients submitted to cancer treatment, such as the use of methotrexate.

Methods

Characterization of the study

A clinical study was conducted at the institute of integrated medicine "Instituto de Medicina Integral Professor Fernando Figueira" from January 2010 to December 2010. A total of 40 patients (27 males and 13 females) in the age-range from 1 to 18 years receiving care at the Pediatric Oncology Unit, were selected. All had acute lymphoblastic leukemia, and received high doses of methotrexate (HDMTX) (2.5 and 5.0 g/m^2) in the consolidation phase.

The protocols for this study were approved by the Ethics Committee of the "Instituto de Medicina Integral Professor Fernando Figueira," Recife, Brazil, under protocol #1562 and were performed at the Pediatric Oncology Unit of this Institute. Throughout the study, the patients were cared for in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2000.

All patients underwent the oral care protocol before starting the oncologic treatment. The oral care protocol included oral examination and preventive dental treatment, and potential sources of infection were assessed and completely eliminated. Standardized methods of oral hygiene were established with the use of soft toothbrushes, toothpaste, and dental floss.

Inclusion criteria

Patients with acute lymphoblastic leukemia and receiving HDMTX (2.5 and 5.0 g/m^2) in the consolidation phase were included.

Exclusion criteria

Patients were excluded from the study if they had active oral, viral, bacterial, or fungal infections, or had active oral bleeding that was uncontrollable during laser therapy. In addition, patients were excluded if they were receiving drugs for the treatment and/or prevention of mucositis.

Study design

The patients were distributed by convenience sampling into two groups (A and B) based on the order in which they were hospitalized. Group A was composed of patients who received preventive laser [red or infrared–subgroups A1 ($n=10$) and A2 ($n=10$), respectively] for 5 days, beginning on the first day of CT. Group B was composed of patients who did not receive any preventive intervention, and those who developed post-CT mucositis were subjected to therapeutic laser [red or infrared–subgroups B1 ($n=10$) and B2 ($n=10$), respectively] until full remission of the lesions.

Group A – preventive laser. Preventive laser was applied at 24 h intervals, with the first application on Day 1 of the CT cycle and continuing up to Day 5 of the cycle.

Group B – therapeutic laser. Therapeutic laser was applied after the diagnosis of OM, at 24 h intervals, until complete remission of the lesions.

Application of low-level laser

The Flash Laser III (DMC™, Plantation, FL) laser equipment was used, at a wavelength of 660 nm (red laser) and wavelength of 830 nm (infrared laser), both with 100 mW power and spot size of 0.028 cm^2.

All applications were performed by a single professional. Irradiations were performed in contact mode, used punctually and perpendicular to the tissue. The tip of the laser was disinfected with 70% alcohol solution and wrapped with a plastic film. Patients and operators wore glasses for eye protection.[2]

In Group A (preventive treatment), specific sites were selected in the oral mucosa: the left and right jugal mucosa (two points on each side), the superior and inferior internal lip mucosa (one point in each quadrant), the floor of the mouth (one point on each side), the lateral edge of the tongue (two points on each side), the tip of the tongue (one point), the soft palate (one point on each side), and the labial commissure.[2] In the soft palate, the laser application was defocused at a distance of $\sim$1.5 cm, with the goal of achieving better patient tolerance.

Each site received 1 J of energy,[11] resulting in an energy density of 35 J/cm^2. The exposure time was 10 sec/point.

In Group B (therapeutic treatment), the laser was directly applied to the mucositis lesions. Each lesion received an application of 2 J of energy,[12] resulting in energy density of 70 J/cm^2, with a 20 sec exposure time per point.

For all protocols, before and after each session the power output was checked using a power meter (Coherent Molectron®, Santa Clara, CA).

Progression

Both groups were evaluated daily using the World Health Organization (WHO)[13] scale: grade 0 = no mucositis; grade I = erythema without lesions; grade II = ulcers, but able to eat; grade III = painful ulcers but able to consume liquid food (nutrition), with analgesia for support; grade IV = requires parenteral or enteral support and continuous analgesia.

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

In Group A, if the patient's mucosa was normal by Day 5, the laser application was discontinued. However, if the

Table 1. Grade of Clinical Mucositis Per Day of Evaluation Per Age Range

	Age range (years)		
Evaluation day	*≤8 years* *Average ± SD (median)*	*>8 years* *Average ± SD (median)*	p *Value*
1	0.00 ± 0.00 (0.00)	0.00 ± 0.00 (0.00)	$p^a = 1.000$
3	0.85 ± 1.01 (0.00)	0.14 ± 0.53 (0.00)	$p^a = 0.030^b$
5	1.08 ± 1.49 (0.00)	0.00 ± 0.00 (0.00)	$p^a = 0.007^b$

[a]Mann–Whitney test.
[b]Significant difference at the level of 5.0%.

patient developed OM, the preventive laser protocol was discontinued and the therapeutic laser protocol was initiated and continued until full remission of lesions.

In Group B, the therapeutic laser protocol was performed when the oral mucositis first appeared through to full remission. If the patient's mucosa was normal by Day 5, no therapy was performed.

In both groups, the patients were evaluated until Day 14.

Results

Patients underwent dental treatment before the CT; in 72.5% of patients, oral health was excellent, and was not correlated with the absence of OM ($p > 0.05$).

Among the 40 patients, 65% were in the age range from 1 to 8 years, with a mean of age 6.83 years, and 67.5% were males.

The overall incidence of oral mucositis was 57.5%; however, among the patients up to 8 years of age, the degree of mucositis was significantly higher than that observed among patients >8 years (Table 1). In both groups, the distribution of the patients up to 8 years of age was similar. In Group A, 12 patients (60%) were <8 years of age, and in Group B, 13 (65%) were <8 years of age.

In Group A, 40% of patients developed OM and in Group B, 75% of patients developed OM. In subgroup A1, only 30% of patients had mucositis; in subgroup A2, 50% had mucositis; in subgroup B1, 70% had mucositis and in subgroup B2 80% had mucositis.

In Group A, 8 patients developed OM: 2 on Day 2, 3 on Day 3, 1 on Day 6, 1 on Day 7, and 1 on Day 8. In Group B, 15 patients developed OM: 3 on Day 2, 4 on Day 3, 3 on Day 4, 1 on Day 5, and 4 on Day 6. Figure 1 shows the degrees of OM in each group at end of study according to WHO parameters. In Group A, no patient developed extensive ulcers and in Group B, 7.5% [3/20: one patient in subgroup B1 (Day 5) and two in subgroup B2 (Day 4 and Day 5)] developed extensive ulcers. In both groups, 75% did not develop pain symptoms, and no patient required nutritional support.

The mean day for onset of oral mucositis was 4 ± 1.8 days, with duration of 2.3 ± 2.6 days, and pain was reported for 0.9 ± 1.9 days irrespective of the group to which the patient belonged.

The Mann–Whitney test showed that there were statistically significant differences between the type of laser (wavelength) with the number of days with pain (p value = 0.033) and severity of mucositis (p value = 0.046) (Fig. 2).

Discussion

Several studies have shown positive results with the use of LLLT in reducing the incidence and severity of OM in patients undergoing anticancer treatment;[1,11,14–20] however, the exact mechanism of interaction of the laser with the tissue is still not completely understood.

It is thought that there is a photobiological phenomenon involving the conversion of the laser light energy input through biochemical and photophysical processes. Photoreceptors

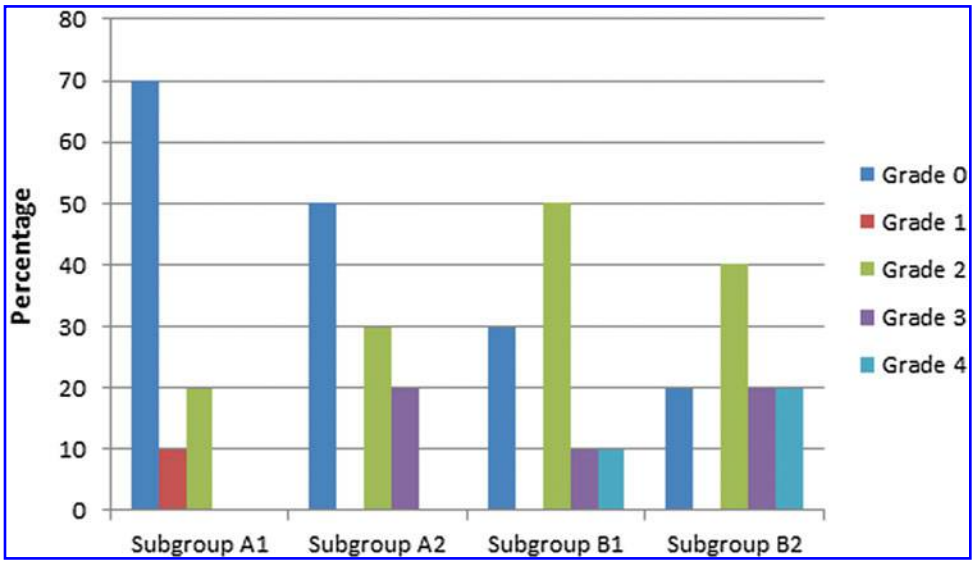

FIG. 1. Distribution of oral mucositis per grade, per subgroup.

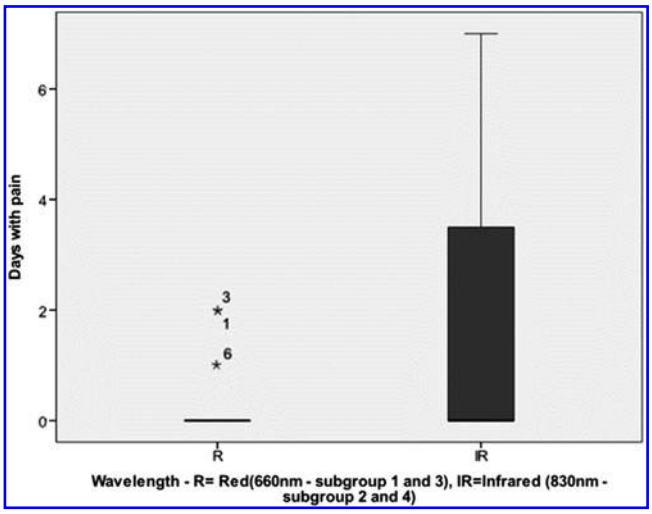

FIG. 2. Boxplot: number of days with pain × wavelength.

absorb certain wavelengths, causing a cascade effect in the respiratory chain, which results in the production of energy to fuel cell metabolic processes with increased cellular proliferation and protein synthesis, promoting tissue repair.[21–25]

Some studies have indicated that laser irradiation can reduce COX-2[26] and pro-inflammatory cytokine IL-1β[27] expression, thereby decreasing the inflammatory response leading to a reduction in neutrophil infiltrate.[26]

The laser therapy protocol used is based on the pathogenesis of mucositis, and the effects of laser phototherapy on angiogenesis and control of oxidative stress are well known. It is also well known that the epithelial damage caused by CT and radiotherapy is preceded by endothelial vascular changes. Laser phototherapy has shown the potential to stimulate angiogenesis, and this may help to heal ulcers, depending upon their size. The appearance of mucositis has also been associated with high levels of TNF-α and IL-13. Laser phototherapy appears to diminish the levels of TNF-α in sites subjected to chronic stress. The initiating events of mucositis are associated with ROS derived from the action of chemotherapy and radiotherapy, which cause damage to the DNA, and the activation of transcription factors, among them nuclear factor-kappa B (NF-kB), which in turn generates the activation of various cytokines (TNF-α, IL-1, and IL-6). Laser phototherapy has been shown to have a blocking effect on ROS and NF-kB activation.[4,6,7,21,23]

Moreover, the use of low laser therapy can influence vascular endothelial growth factor production and, therefore, angiogenesis.[28,29]

Furthermore, laser helps to increase protein synthesis within cells, increases cell proliferation and alterations in cell cycle control and apoptosis,[30] stimulates DNA synthesis in myofibroblasts without degenerative changes, and could transform fibroblasts into myofibroblasts.[31] It induces collagen deposition with increased collagen orientation and maturation, which has more stability and tensile strength,[8,20,32] which may promote and activate the epithelial healing of the mucosa.

A number of clinical studies have reported the benefits of LLLT, including lasers and LEDs, in preventing oral mucositis and reducing OM pain. It may be used alone, or combined with drug treatment, because it provides pain relief, comfort to the patient, control of inflammation, maintenance of the mucosa integrity, and better tissue repair.[14,15,25,26,33–38]

Perhaps these mechanisms may explain the pain relief, delay in the onset of ulcers, and reduction in the duration of the lesions reported by Caballero et al.,[1] which was confirmed in the present study with reduction in the average duration of OM that occurred in both groups.

Barasch et al.[11] applied LLLT at a wavelength of 632.8 nm, 25 mW and 1 J/cm^2 energy density in patients who were given a high dose of CT before hematopoietic stem cell transplantation (HSCT) or chemoradiotherapy, and obtained the effect of reducing the severity of OM. Sandoval et al.[12] used 660 nm and reported immediate pain relief with 2 J/cm^2 energy density. In our study, we applied 1 J/cm^2 energy density in the prophylactic group and 2 J/cm^2 in the therapeutic group, obtaining similar results.

Although the pain data must be interpreted with some caution, points can be made about the effects of prophylactic laser therapy on OM pain. In this study, the reduction in pain was greatest in subgroup A1, which received red light preventively (90%), thereby confirming the results of the clinical evaluation. This would most probably seem to be the result of the decrease in the severity of mucosal damage in the 660 nm laser group, and has been noted in other reports.[35–37]

Our results showed that the degree of mucositis in patients up to 8 years of age was significantly higher than that observed among patients >8 years, irrespective of the group to which the patient belonged. These results seem to support the theory that younger patients appear to be at greater risk of CT-induced OM, because their epithelium has a higher mitotic rate and more epidermal growth factor receptors.[1,15] Nevertheless, the role of genetic polymorphisms in oral toxicity risk is still unclear, and mechanistic gene-based risk research for OM is still in its infancy.[39]

The difficulty of demonstrating the efficacy of laser in oncologic patients with OM results from the variety of types of disease and CT, and radiotherapy protocols.[2] Furthermore, the parameters of LLLT reported in the studies vary significantly with regard to types of laser sources, wavelengths, and energy densities.[16]

In an important meta-analysis, Bensadoun et al.[25] demonstrated moderate-to-strong evidence in favor of clinically relevant effects when LLLT is applied at optimal doses in cancer therapy-induced OM, and recommends red or infrared LLLT with an output between 10 and 100 mW, with spot size not exceeding 1 cm^2; an energy density of 2–3 J/cm^2, resulting in an energy of 2–3 J for prophylaxis, and 4 J/cm^2 resulting an energy of 4 J for a therapeutic effect; application on a single spot rather than in scanning motion; and therapy repeated daily or every other day, or a minimum of three times per week until resolution is achieved.

In the present study, laser was used at wavelengths of 660 and 830 nm with an output of 100 mW, energy of 1 J, resulting in an energy density of 35 J/cm^2 for 10 sec in the prophylactic group, and energy of 2 J, resulting in energy density of 70 J/cm^2 for 20 sec in the therapeutic group. We used the same energies recommended by Bensadoun et al.,[25] but because of the small spot size, the energy densities were much higher than those used in their research.

The clinical evaluation revealed that LLLT was effective in preventing or reducing the incidence of OM, with a

significant difference detected by the end of the study. The results suggest that laser phototherapy had a positive effect on reducing mucositis severity in pediatric patients undergoing cancer treatment.

Conclusions

For children undergoing cancer treatment with HDMTX, LLLT proved to be effective in the treatment and prevention of OM. Prophylactic treatment was more effective than treating after symptoms appeared. No significant difference was found between 660 and 830 nm wavelengths.

Author Disclosure Statement

No competing financial interests exist.

References

1. Caballero, A.R., Lagares, D.T., García, M.R., Ibáñez, J.P., Padilla, D.G., and Pérez, J.L.G. (2012). Cancer treatment-induced oral mucositis: a critical review. Int. J. Oral Maxillofac. Surg. 4, 225–238.
2. Abramoff, M.M.F., Lopes, N.N.F., Lopes, L.A., et al. (2008). Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. Photomed. Laser Surg. 26, 393–400.
3. Elting, L.S., Keefe, D.M., Sonis, S.T., et al. (2008). Burden of Illness Head and Neck Writing Committee. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. Cancer 113, 2704–2713.
4. Sonis, S.T. (2004). The pathobiology of mucositis. Nat. Rev. Cancer 4, 277–284.
5. Sonis, S.T. (1998). Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol. 34, 39–43.
6. Sonis, S.T. (2002). The biologic role of nuclear factor-$\kappa\beta$ in disease and its potential involvement in mucosal injury associated with antineoplastic therapy. Crit. Rev. Oral Biol. Med. 13, 300–309.
7. Sonis, S.T. (2007). Pathobiology of oral mucositis: novel insights and opportunities. J. Support. Oncol. 5, 3–11.
8. França, C.M., França, C.M., Núñez, S.C., et al. (2009). Low-intensity red laser on the prevention and treatment of induced-oral mucositis in hamsters. J. Photochem. Photobiol. B. Biol. 94, 25–31.
9. Carvalho, P.A.G., Jaguar, G.C., Pellizzon, A.C., Prado, J.D., Lopes, R.N., and Alves, F.A. (2011). Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. Oral Oncol. 47, 1176–1181.
10. Clarkson, J.E., Worthington, H.V., Furness, S., McCabe, M., Khalid, T., and Meyer, S. (2010). Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst. Rev. 4, CD001973.
11. Barasch, A., Peterson, D.E., Tanzer, J.M., et al. (1995). He–Ne laser effects on conditioning-induced oral mucositis in bone marrow transplantation patients. Cancer 76, 2550–2556.
12. Sandoval, R.L., Koga, D.H., Buloto, L.S., Suzuki, R., and Dib, L.L. (2003). Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital. J. Appl. Oral Sci. 11, 337–341.
13. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization, 1979.
14. Cowen, D., Tardieu, C., Schubert, M., et al. (1997). Low energy He–Ne laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of double blind randomized trial. Int. J. Radiat. Oncol. Biol. Phys. 38, 697–703.
15. Antunes, H.S., Azevedo, A.M., da Silva Bouzas, L.F., Adao, C.A., Pinheiro, C.T., Mayhe, R., et al. (2007). Low-power laser in the prevention of induced oral mucositis in bone-marrow transplantation patients: a randomized trial. Blood 190, 2250–2255.
16. Jaguar, G.C., Prado, J.D., Nishimoto, I.N., et al. (2007). Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation. Oral Dis. 13, 538–543.
17. Silva, G.B.L., Mendonça, E.F., Bariani, C., Antunes, H.S., and Silva, M.A.G. (2011). The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. Photomed. Laser Surg. 29, 27–31.
18. Carvalho, P.A.G., Jaguar, G.C., Pellizzon, A.C., Prado, J.D., Lopes, R.N., and Alves, F.A. (2011). Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. Oral Oncol. 47, 1176–1181.
19. Bjordal, J.M., Bensadoun, R.J., Tunér, J., Frigo, L., Gjerde, K., and Lopes-Martins, R.A.B. (2011). A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. Support. Care Cancer 19, 1069–1077.
20. Gautam, A.P., Fernandes, D.J., Vidyasagar, M.S., Maiya, A.G., and Vadhiraja, B.M. (2012). Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients – A triple blinded randomized controlled trial. Radiother Oncol. Available at: http://dx.doi.org/10.1016/j.radonc.2012.06.011.
21. Karu, T. (1986). Molecular mechanism of the therapeutic effect of low-intensity laser radiation. Dokl Akad Nauk SSSR 291, 1245–1249.
22. Karu, T., Ryabykh, T.P., Fedoseyeva, G.E., et al. (1989). Helium- neon laser-induced respiratory burst of phagocyte cells. Lasers Surg. Med. 9, 585–588.
23. Karu, T. (1989). Photobiology of lower laser effects. Health Phys. 56, 691–704.
24. Karu, T. (1999). Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J. Photochem. Photobiol. B. Biol. 49, 1–17.
25. Bensadoun, R.J., and Nair, R.G. (2012). Low-level laser therapy in the prevention and treatment of cancer therapy-induced mucositis: 2012 state of the art based on literature review and meta-analysis. Curr. Opin. Oncol. 24, 363–370.
26. Lopes, N.N.F., Plapler, H., Chavantes, M.C., Lalla, R.V., Yoshimura, E.M., and Alves, M.T.S. (2009). Cyclooxygenase-2 and vascular endothelial growth factor expression in 5-flourouracil-induced oral mucositis in hamster: evaluation of two low-intensity laser protocols. Support. Care Cancer 17, 1409–1415.
27. Gavish, L., Perez, L., and Gertz, S.D. (2006). Low-level laser irradiation modulates matrix metalloproteinase activity and gene expression in porcine aortic smooth muscle cells. Lasers Surg. Med. 38, 779–786.
28. Zhang, W.G., Wu, C.Y., Pan, W.X., Tian, L., and Xia, J.L. (2004). Low-power helium-neon laser irradiation enhances

the expression of VEGF in murine myocardium. Chin. Med. J. 117, 1476–1480.
29. Kipshidze, N., Nikolaychik, V., Keelan, M.H., et al. (2005). Low-power helium: neon laser irradiation enhances production of vascular endothelial growth factor and promotes growth of endothelial cells in vitro. Lasers Surg. Med. 28, 355–364.
30. Gao, X., and Xing, D. (2009). Molecular mechanisms of cell proliferation induced by low power laser irradiation. J. Biomed. Sci. 16, 4.
31. Pourreau-Schneider, N., Ahmed, A., Soudry, M., Jacquemier, J., Kopp, F., Franquin, J.C., and Martin, P.M. (1990). Helium-neon laser treatment transforms fibroblasts into myofibroblasts. Am. J. Pathol. 137, 171–178.
32. Corazza, A.V., Jorge, J., Kurachi, C., and Bagnato, V.S. (2007). Photobiomodulation on the angiogenesis of skin wounds in rats using different light sources. Photomed. Laser Surg. 25, 102–105.
33. Ferreira, D.M., Zângaro, R.A., Balbin Villaverde, A., et al. (2005). Analgesic effect of He-Ne (632.8 nm) low-level laser therapy on acute inflammatory pain. Photomed. Laser Surg. 23, 177–181.
34. Laakso, E., and Cabot, P.J. (2005). Nociceptive scores and endorphin- containing cells reduced by low-level laser therapy (LLLT) in inflamed paws of Wistar rat. Photomed. Laser Surg. 23, 32–35.
35. Bjordal, M.J., Johnson, M.I., Iversen, V., et al. (2006). Low-level laser therapy in acute pain: A systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. Photomed. Laser Surg. 24, 158–168.
36. Migliorati, C., Massumoto, C., Eduardo, F.P., et al. (2001). Low-energy laser therapy in oral mucositis. Science. 1, 97–100.
37. Nes, A.G., and Posso, M.B. (2005). Patients with moderate chemotherapy-induced mucositis: pain therapy using low intensity lasers. Int. Nurs. Rev. 52, 68–72.
38. Schubert, M.M., Eduardo, F.P., Guthrie, K.A., et al. (2007). A phase III randomized double-blind placebo-controlled clinical trial to determine the efficacy of low level laser therapy for the prevention of oral mucositis in patients undergoing hematopoietic cell transplantation. Support. Care Cancer 15, 1145–1154.
39. Cheng, K.K.F., Lee V., Li C.H., Goggins W., Thompson D.R., Yuen H.L., and Epstein J.B. (2011). Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. Oral Oncol. 47, 153–162.

Address correspondence to:
Andreza Veruska Lira Correia
Postgraduate Program in Dentistry
Oral Pathology Unit
Federal University of Pernambuco
Recife, Pernambuco
Brazil

E-mail: andrezalira@gmail.com