

Low-level Infrared Laser Therapy to Prevent Radiotherapy-induced Oral Mucositis: A Randomized Placebo-controlled Study

Alessandra Kuhn^a, Gilberto Heinzmann^b, César A. da Silva^c, Julio C. Stobbe^c, Marcos A. Knack^a, Alexandre Basualdo^a, Fabrício B. Branda^b, Giana F. Kuhn^d, Eduardo Dall' Magro^e

^a Professor and Surgeon, Oncology Unit, São Vicente de Paulo Hospital, Passo Fundo, RS, Brazil; Oral and Maxillofacial Surgery Unit, São Vicente de Paulo Hospital, Passo Fundo, RS, Brazil.

^b Dentist, Oral and Maxillofacial Surgery Unit, São Vicente de Paulo Hospital, Passo Fundo, RS, Brazil.

^c Medical Doctor, Oncology Unit, São Vicente de Paulo Hospital, Passo Fundo, RS, Brazil.

^d Graduate Student, Passo Fundo University, School of Medicine, Passo Fundo, RS, Brazil.

^e Professor, Passo Fundo University, School of Dentistry, Passo Fundo, RS, Brazil.

Purpose: This study was conducted to evaluate low-level infrared laser therapy (LLLT) for prevention of radiotherapy-induced oral mucositis (OM).

Patients and Methods: The trial was open to patients with carcinoma of the hypopharynx, oropharynx, and oral cavity, who had been treated by external radiotherapy with a total dose of 80 Gy at a rate of 1 fraction of 2 Gy/day, 5 days a week, from a linear photon accelerator between Oct. 2006 and Oct. 2007. A placebo-controlled randomized trial was carried out using LLLT (GaAIs) or placebo (sham treatment) daily for five consecutive days during the weeks of head and neck radiotherapy. The 30 treatment areas included: buccal mucosa, palate, tonsillar pillars, tongue, and neck. The LLLT group was treated with GaAIs laser, wavelength (λ): 830 nm (infrared), power: 100 mW, dose: 4 J/cm², and the placebo group underwent sham treatment. OM was clinically assessed by the WHO scale and a segmented visual analog scale (VAS) for pain (patient self-evaluation).

Results: Thirty patients were eligible for the study but only 23 completed the treatment and were available for analysis. The mean age was 54 (\pm 17) years. Eleven patients were randomized in the laser group and twelve patients in the placebo-control group. Patients had daily OM grading assessments and pain measurement before laser or sham application. During the 6 weeks of radiotherapy, the mean grade of OM in laser group was significantly lower ($p < 0.002$) than the mean grade in the placebo group. The pain score after each laser or placebo application was significantly lower ($p < 0.006$) in the laser group during the same period.

Conclusion: Our study has shown evidence that laser therapy in addition to oral care can decrease the severity of radiotherapy-induced OM and pain. It should encourage clinicians to use this technique to improve quality of life of cancer patients during oncology treatment.

Keywords: mucositis, radiotherapy, head and neck cancer, low-level laser therapy.

J Oral Laser Applications 2008; 8: 219-224.

Submitted for publication: 25.09.08; accepted for publication: 28.11.08.

Each year, approximately 500,000 new cases of head and neck cancer (HNC) are diagnosed worldwide.¹ The treatment of choice consists of surgery, radiation,

and combined surgery/radiation. Recently, chemotherapy (CT) has been used as a neoadjuvant treatment, as adjuvant treatment after definite surgery and/or radia-

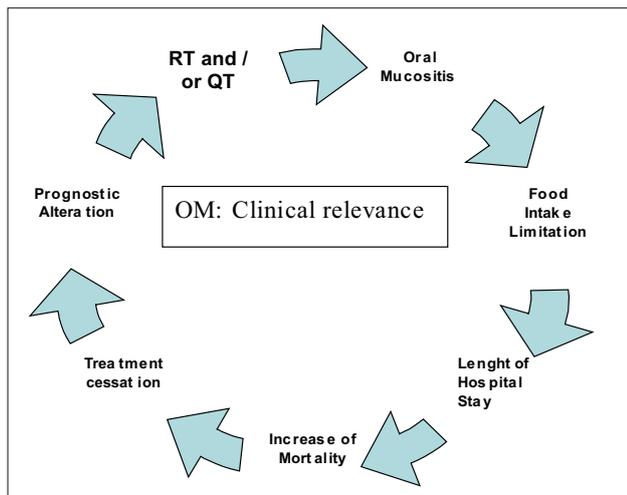


Fig 1 Clinical relevance of OM.

tion, or concurrent with both definite and adjuvant radiotherapy (RT).^{1,2}

Although RT plays an important role in the management of patients with HNC, it is also associated with several undesired side effects. Frequently, jaws, salivary glands, and oral mucosa will be included in the RT field. Changes induced by exposure to radiation may occur during and after completion of therapy, including oral mucositis (OM), candidiasis, osteoradionecrosis, and radiation caries.^{1,3,4} However, the precise incidence and prevalence of RT-induced side effects and sequelae are still difficult to obtain, with rates ranging from 13% to 89%.⁵

Patients with HNC receiving combined treatment with RT and CT experience severe OM, recognized as one of the principal dose limiting factors during oncology treatment. Severe OM causes considerable pain and discomfort, leading to a high need for pain medication, parenteral nutrition, longer hospital stays, and higher cost of care (Fig 1).⁶ Pathologic evaluation of OM reveals mucosal thinning, leading to a shallow ulcer thought to be caused by inflammation and depletion of the epithelial basal layer with subsequent denudation and bacterial infection.⁷ The wound healing response to this injury is characterized by inflammatory cell infiltration, interstitial exudates, fibrin, and cell debris, producing a pseudomembrane analogous to the scar of superficial skin wounds.^{7,8} So far, there is no standard effective prophylaxis or therapy for this condition, with the possible exception of low-level laser therapy (LLLT).⁹ Irradiation with laser has been reported to be a simple atraumatic technique useful due to its effects:

healing of chronic wounds ($\lambda = 632.8$ nm and 780 to 900 nm), analgesia ($\lambda = 630$ to 650 nm and 780 to 900 nm) and anti-inflammation (same wavelengths), all shown by physical, biological, and experimental studies.^{6,7,9}

Barasch et al¹⁰ used laser (He-Ne, 632.8 nm, 35 mW, 1 J/cm²) prophylactically in 20 cancer patients. They received laser to the right or left of midline; the contralateral side was sham treated and served as a control. Patients were treated daily for 5 consecutive days, beginning the day after cessation of chemotherapy. OM and pain scores were significantly lower for the treated side. Benzadoun et al⁸ conducted a randomized multicenter trial to investigate the effectiveness of laser (He-Ne, 632.8 nm, 60 mW, 2 J/cm²) for the prevention of radiation-induced OM in patients with head and neck cancer. Patients treated with laser showed both pain relief and OM reduction compared to the placebo group. Maiya et al¹¹ showed positive results of laser (He-Ne, 632.8 nm, 10 mW, 1.8 J/cm²) in a randomized control studying HNC patients for prevention of OM. A total of 50 patients, 25 per group, were treated with laser or oral care. The result showed a significant difference in pain and mucositis. In the paper by Ness and Posso,¹² the authors investigated the effect of LLLT (GaAlAs, 830 nm, 250 mW, 35 J/cm²) on pain relief among adults patients who developed chemotherapy-induced OM. The patients were treated for 5 days and pain was measured before and after each session of laser application. There was a significant decrease in daily average experience of pain felt before and after each treatment, confirming that LLLT can relieve pain among patients who have developed OM.

The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology published clinical practice guidelines for evidence-based management of OM during CT and RT. In addition to basic oral care, mucosal coating agents, analgesics, and growth factors (KGF- α), LLLT is regarded as a very promising investigational method, based on its current encouraging results (level of evidence II, grade of recommendation B).¹³

We decided therefore to conduct this randomized placebo-controlled study to determine whether prophylactic infrared LLLT (GaAlAs, 830 nm, 100 mW, 4 J/cm²) could prevent radiotherapy-induced OM.

PATIENTS AND METHODS

This study was carried out at the Oncology Unit (OU) of the Hospital São Vicente de Paulo (HSVP). From

Table 1 Characteristics of patients

Patient	Age	Sex	Cancer diagnosis	Groups: Laser(L+) Sham(L-)	RT (Gy)	Adjuvant CT
1	44	M	Tongue	L-	45 Gy + 18 Gy	-
2	48	M	Oropharynx	L-	50 Gy + 21 Gy	+
3	72	M	Hypopharynx	L+	45 Gy + 25 Gy	-
4	45	F	Oropharynx	L+	45 Gy + 25 Gy	+
5	45	M	Tongue	L+	45 Gy + 25 Gy	+
6	61	M	Oropharynx	L-	45 Gy + 5.4 Gy	-
7	67	M	Oropharynx	L+	50 Gy	+
8	79	F	Oropharynx	L-	45 Gy + 25 Gy	-
9	65	M	Oropharynx	L-	55 Gy + 25 Gy	-
10	69	M	Jaw	L+	36 Gy	-
11	62	M	Oropharynx	L+	45 Gy + 25 Gy	-
13	47	F	Oropharynx	L+	45 Gy	-
14	58	M	Oropharynx	L-	45 Gy + 25 Gy	+
15	42	M	Tongue	L-	45 Gy + 25 Gy	-
16	48	M	Palate	L-	45 Gy + 5.4 Gy	-
17	43	M	Palate	L-	45 Gy + 5.4 Gy	-
18	77	M	Oropharynx	L-	45 Gy + 25 Gy	-
19	84	M	Oropharynx	L-	45 Gy + 20 Gy	-
20	18	F	Cranio	L-	45 Gy + 9 Gy	-
21	50	M	Oropharynx	L+	45 Gy + 5.4 Gy	-
22	65	M	Hypopharynx	L+	45 Gy + 25 Gy	+
23	45	M	Oropharynx	L+	45 Gy + 25 Gy	+

October 2006 to October 2007, all consecutive HNC patients with carcinoma of the oropharynx, hypopharynx, and oral cavity who had been treated by external radiotherapy were eligible for this trial. The study was approved by the Ethics Committees of the HSVP of Passo Fundo.

Thirty patients were eligible for the study, but only 23 completed the treatment and were available for analysis. The mean age was 54 (± 17) years. Eleven patients were randomized in the laser group and 12 patients in the placebo-control group. Patients treated with RT received a total dose of 80 Gy at a rate of 1 fraction of 2 Gy/day, 5 days a week, prescribed according to the International Commission on Radiation Unit and Measurements.

Patients' characteristics are detailed in Table 1. The laser and sham groups were similar in relation to gender and disease groups.

Before starting RT, all patients at the OU received a routine odontological assessment, including removal of septic teeth and oral recommendations to brush teeth using a soft toothbrush and neutral toothpaste after

every meal. In addition, patients were recommended to use a 0.05% fluoride mouthrinse (Oral B) twice a day (after breakfast and before going to bed at night). During RT, patients received additional reminders and instructions to reinforce compliance with the initial recommendations on tooth brushing and mouth washing.

Radiotherapy

Patients received a total dose of 80 Gy at a rate of 1 fraction of 2 Gy/day, 5 days a week from a linear photon accelerator, model Primus (Siemens), in accordance with the International Commission on Radiation Unit and Measurements without prior surgery or concomitant chemotherapy (Table 1).

Randomization

Once started RT, all patients received intervention 5 days a week. The 30 treatment areas included: buccal mu-

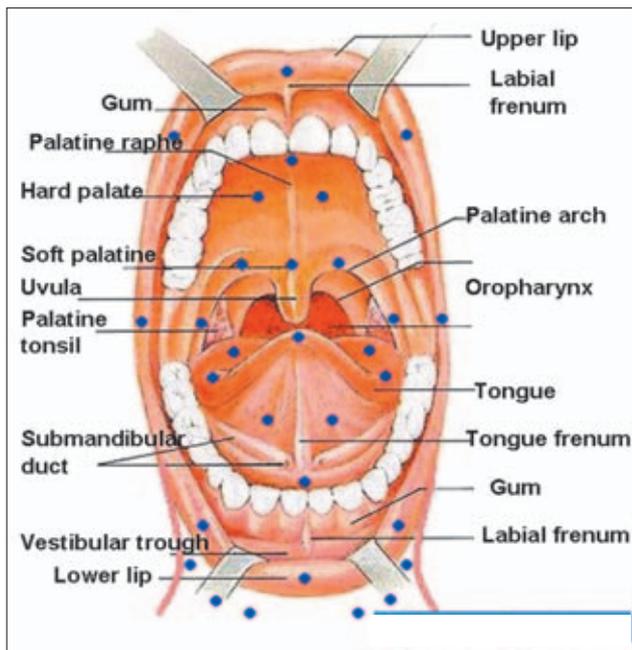


Fig 2 Intervention points.

cosa, palate, tonsillar pillars, tongue, and neck as shown in Fig 2. The patients were divided into 2 groups by a computer-generated code:

Group A: Patients received laser therapy with a GaAlAs unit (Flash Lase, Dental Manufactory Company (DMC) Equipment; São Carlos, SP, Brazil) with a continuous 830 nm wavelength, 100 mW power, dose 4 J/cm². The laser was operated by a trained dentist from the OU. The dentist who applied laser did not participate in the evaluation and measuring of OM. International safety procedures for laser use were followed in this study and are considered an important routine in our department.

Group B: Patients received a placebo application (sham treatment). Only the handpiece was used, the laser was not turned on.

All patients had a daily oral examination before laser or sham applications.

Definition and Scoring of OM and Pain

OM grade was scored by the same investigator, a dentist who was blind to the randomization, using the WHO scale¹⁴ and VAS¹⁵ for pain after each laser or sham application.

Statistical Analysis

The statistical analysis was carried out using descriptive statistics including median, mean, standard deviation, and percentiles for the variables age, localization and grade of OM, odontological assessment and diagnosis of the tumors.

To compare the two groups, we analyzed the data on gender and disease as frequencies and percentages. Concordance or differences in the frequency distribution between the two groups were tested using the Student t-test.

A level of significance of 5% was used and data were analyzed using SPSS (Chicago, IL, USA), version 14.0.

RESULTS

Oral Mucositis and Pain

LLLT applications were well tolerated and there were no adverse side effects attributable to its use. Buccal mucosa (70%), lateral/ventral tongue (58%) and lips (36%) were the most frequent sites affected.

The absolute frequency of OM grades between groups after 7, 15, and 30 days of intervention is depicted in Fig 3. In the laser group, after 7 days of intervention (second week of RT), 4 of 11 patients developed OM while 2 of 12 did in the sham group. On day 15, (third week of RT) 5 of 11 patients presented OM in the laser group and 10 of 12 in the sham group. After 30 days of intervention (6 weeks), the proportion of OM patients in the laser group was 4 of 11 and in sham group 11 of 12.

The results showed a significant difference in OM and pain between the two groups. At the end of radiotherapy (6 weeks), mean pain ($p < 0.006$) and OM grade ($p < 0.002$) were significantly lower in the study group compared with control (Figs 4 and 5).

DISCUSSION

Low-level laser photostimulation has been used as a treatment modality for various medical problems, including wound repair processes, musculoskeletal complications, and pain control. Clinical studies have shown low energy lasers to be effective as analgesics, and to accelerate the healing of injured tissue.^{16,17} We conducted this study to find out its efficacy on radiation-induced mucositis in head and neck cancer patients using a different protocol (GaAlAs, 830 nm, 100 mW,

Fig 3 OM measurement after 7, 15 and 30 days of intervention. Observe the OM graduation between groups and the absolute frequency of patients in each group.

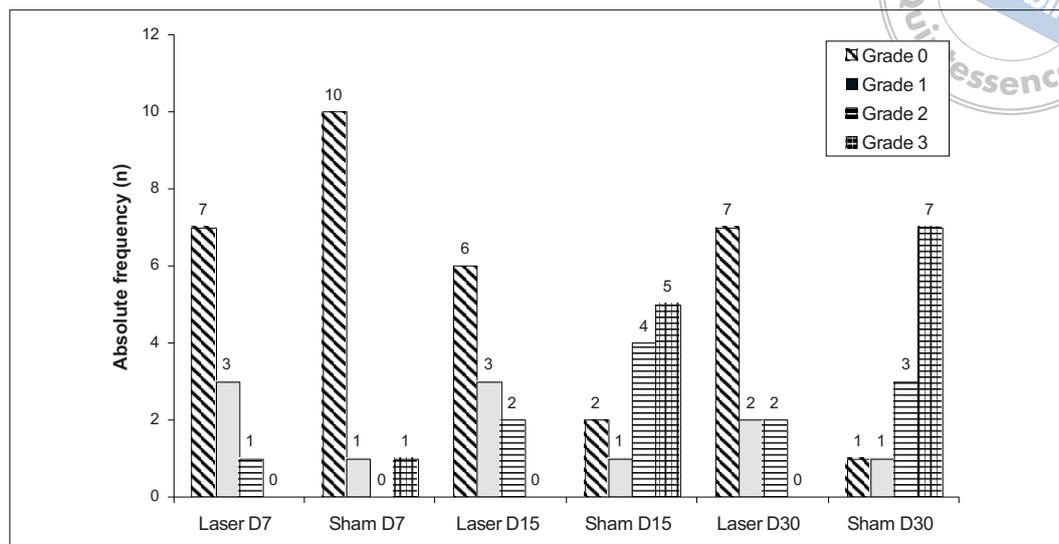


Fig 4 OM measurement between groups from the start of RT to 6 weeks of treatment ($p < 0.002$).

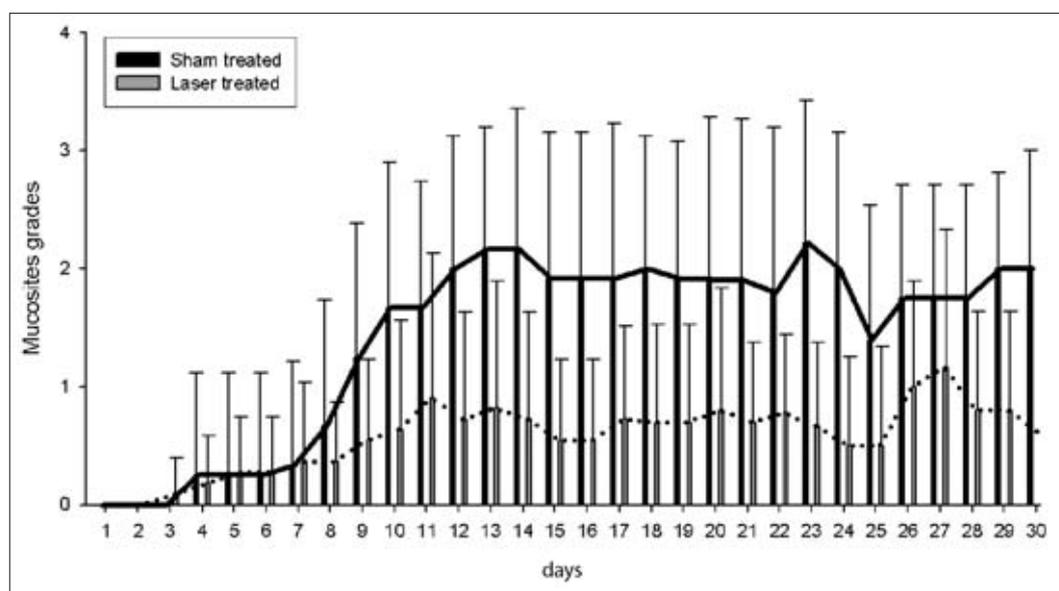
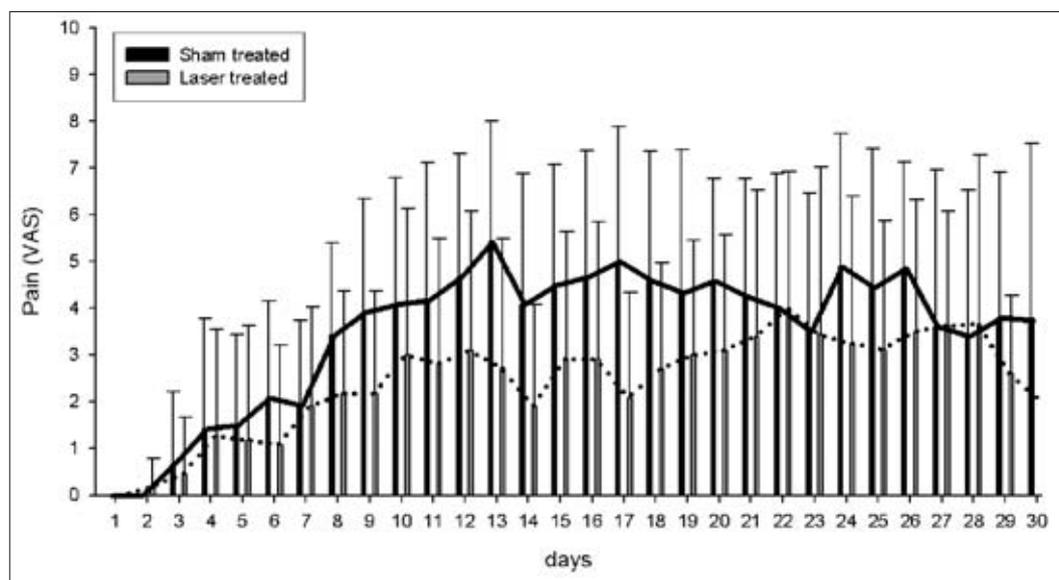


Fig 5 Pain measurement (patient self-evaluation) by VAS (0-10) between groups from the start of RT until 6 weeks of treatment ($p < 0.006$).





4 J/cm²). All patients tolerated the laser treatment without any adverse effect or reactions. However, it is important to emphasize the use of wavelength-specific goggles during the laser application for both patients and the treating dentist to prevent retinal damage by laser. Our results showed that LLLT was effective in reducing OM ($p < 0.002$) and pain ($p < 0.006$) in the patients at the completion of RT (Figs 4 and 5).

The laser application delayed the time of onset, attenuated the peak severity and shortened the duration of OM.⁶ The possible mechanism could be due to the anti-inflammatory and analgesic effect of the laser irradiation on the local tissue, which in turn increases the vascularity and re-epithelization of injured tissue. In oral tissues, the laser applications could stimulate DNA synthesis in myofibroblasts, without degenerative changes, and could transform fibroblasts into myofibroblasts, which may promote and activate the epithelial healing of mucosa. Another mechanism that has been proposed for pain relief is the modulation of pain perception by modification of nerve conduction via release of endorphins and enkephalins.¹¹

Low-level GaAlAs laser therapy during the RT was found to be effective in preventing and treating OM and relieving pain in head and neck cancer patients.

CONCLUSION

Our study has shown evidence that LLLT in addition to oral care can decrease the severity of RT-induced OM and pain. It should encourage clinicians to use this technique to improve the quality of life of cancer patients during oncology treatment.

ACKNOWLEDGMENTS

We would like to thank DMC Equipment (São Carlos, SP, Brazil) and Oral B for their financial support.

REFERENCES

1. Jham BC, Reis PM, Miranda EL et al. Oral health status of 207 head and neck cancer patients before, during and after radiotherapy. *Clin Oral Invest* 2008;12:19-24.
2. Adelstein DJ. Systemic chemotherapy for squamous cell head and neck cancer. *Expert Opin Pharmacother* 2003;4:2151-2163.
3. Ramirez-Amador V, Silverman S, Mayer P et al. Candidal colonization and oral candidiasis in patients undergoing oral and pharyngeal radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:149-153.
4. Vissink A, Burlage FR, Spijkervet FK et al. Prevention and treatment of the consequences of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003;14:213-225.
5. Ohrn KE, Wahlin YB, Sjoden PO. Oral status during radiotherapy and chemotherapy: a descriptive study of patient experiences and the occurrence of oral complications. *Support Care Cancer* 2001;9:247-257.
6. Kuhn A, Vacaro G, Almeida D et al. Low-level infrared laser therapy for chemo- or radiotherapy-induced oral mucositis: a randomized, placebo-controlled study. *J Oral Laser Applic*;2007: 7:175-181.
7. Sonis ST. A biological approach to mucositis. *J Support Oncol* 2004;2:21-36.
8. Bensadoun, RB et al. Low-energy He-Ne laser in the prevention of radiation-induced mucositis. *Support Care Cancer* 1999;7:244-252.
9. Genot MT, Klastersky J. Low-level laser for prevention and therapy of oral mucositis induced by chemotherapy or radiotherapy. *Current Opin Oncol* 2005;17:236-240.
10. Barasch A, Peterson DE. Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. *Oral Oncology* 2003;39: 91-100.
11. Maiya GA, Sagar MS, Fernandes D. Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients. *Indian J Med Res* 2006;126:399-402.
12. Nes AG, Posso MBS. Patients with moderate chemotherapy-induced mucositis: pain therapy using low intensity lasers. *Int Nursing Rev* 2005;52:68-72.
13. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer Suppl* 2004;100:2026-2046.
14. World Health Organization. Handbook for Reporting Results of Cancer Treatment. Geneva: Offset Publication, 1979;48:15-22.
15. Langley GB; Sheppard H. The visual analogue scale: Its use in pain measurement. *Rheumatol Int* 1985;5:145-148.
16. Fahey TJ, Sadaty A, Jones WG et al. Diabetes impairs the late inflammatory response to wound healing. *J Surg Res* 1991;50:308-313.
17. Mester E, Mester AF, Mester A. The biomedical effects of laser application. *Lasers Surg Med* 1985;5:31-39.

Contact address: Alessandra Kuhn, Rua Paissandu 641/803, Passo Fundo – RS, 99010-100 Brazil. Tel/Fax: +55(54)2103-5110/8111-9877. e-mail: alessandrakuhn@hotmail.com