Low-level Infrared Laser Therapy in Chemotherapy-induced Oral Mucositis

A Randomized Placebo-controlled Trial in Children

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Background: Oral mucositis (OM) is one of the most frequent complications of chemotherapy for which there is no standard therapy; treatment is mostly conservative. This study was conducted to determine whether low-intensity laser therapy (LLLT) can reduce the duration of chemotherapy-induced OM.

Procedure: A placebo-controlled randomized trial was carried out using LLLT or placebo (sham treatment). Children and adolescents with cancer receiving chemotherapy or hematopoietic stem-cell transplantation between October 2005 and May 2006 were eligible as soon as they developed OM. Patients received intervention for 5 days. The LLLT group was treated with laser GaAlAs, wavelength (λ): 830 nm (infrared), power: 100 mW, dose: 4 J/cm^2, and placebo group underwent sham treatment. The grade of OM was clinically assessed by the National Cancer Institute, Common Toxicity Criteria scale.

Results: Twenty-one patients developed OM and were evaluable for analysis; 18 (86%) patients had a diagnosis of leukemia or lymphoma and 3(14%) had solid tumors. The mean age was 8.2 ($\pm$ 3.1) years. Nine patients were randomized in the laser group and 12 in the placebo-control group. Once OM was diagnosed, the patients had daily OM grading assessments before laser or sham application and thereafter until complete healing of the lesions. On day 7 after OM diagnosis, 1/9 of patients remained with lesions in laser group and 9/12 of patients in the placebo-control group ($P = 0.029$). In the laser group, the mean of OM duration was 5.8 ± 2 days and in the placebo group was 8.9 ± 2.4 days ($P = 0.004$).

Conclusions: Our study has shown evidence that laser therapy in addition to oral care can decrease the duration of chemotherapy-induced OM. Our results confirm the promising results observed in adult cancer patients and should encourage pediatric oncologists to use laser therapy as first-line option in children with chemotherapy-induced OM.

Key Words: children, support care, chemotherapy, mucositis laser

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Oral mucositis is one of the most frequent complications after chemotherapy, occurring in approximately 52% to 80% of children receiving treatment for cancer. The chemotherapeutic regimen, the type of malignancy, patient's age, neutrophil count, and use of oral care measures, are thought to be important factors for the development OM in cancer patients.[1–4]

The pathophysiology of OM is a multistep process, and is not simply cytotoxic damage to the epithelium. It might be initiated by reactive oxygen species that activate transcription factors such as nuclear factor kB and increase production of proinflammatory cytokines leading to epithelial injury and apoptosis.[4]

Sonis[4] identified 5 phases of mucosal injury: initiation, upregulation and generation of messengers, signaling and amplification, ulceration with inflammation, and healing. Pathologic evaluation of OM reveled 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. 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 eschar of superficial skin wound.

Poor oral hygiene, preexisting mouth damage, impaired immune status, and high levels of proinflammatory cytokines predispose patients to severe OM.[5]

The oral cavity is a unique environment in which antimicrobial peptides play a key role in maintaining health and may have future therapeutic applications. Present evidence suggests that α-defencins, β-defensins, LL-37, histatin, and other antimicrobial peptides and proteins have distinct but overlapping roles in maintaining oral health and preventing bacterial, fungal, and viral adherence and infection.[6] Certain genetic polymorphisms may alter the expression or function of defensins and could lead to altered susceptibility to OM.[7] Polymorphisms in gene promoters may underlie genetic susceptibility to chemotherapy-induced toxicities.[6] Future genomic research will uncover fundamental signaling pathways that are involved in the pathologic processes of OM.

Factors predictive for OM included mucositis with a previous cycle of treatment and previous gastritis. In addition, OM is associated with other significant health and economic costs. In the hematopoietic stem-cell transplantation (HSCT) population, it is associated with more days of fever, increased risk of significant infection, higher use of total parenteral nutrition, more days of narcotic administration, and longer hospital stays.[8–12]

At present, there is no standard therapy for OM. Treatment is mostly supportive, consisting of good oral hygiene, mouthwashes, and analgesia. Evidence from

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randomized trials suggests that use of oral chips (criotherapy) for 30 minutes before chemotherapy improves OM in patients who receive 5 days injections of fluorouracil every 28 days, probably through decrease local blood flow and decrease drug absorption.[13] Recombinant human keratinocyte grow factor (palifermin) has also been suggested as having a role to treat OM as it stimulates proliferation and modifies differentiation in epithelial cells, including those of the oral mucosa; hence, this growth factor may be a good candidate for reduction of the mucosal injury caused by radiotherapy or radiochemotherapy.[14–17] Although these strategies seem to work on the healing process, they have limited clinical applications.

Irradiation with laser is a simple nontraumatic technique with the following properties: healing of chronic wounds ($\lambda = 632.8$ nm and 780 to 900 nm), analgesic ($\lambda = 630$ to 650 nm and 780 to 900 nm) and anti-inflamatory (same wavelengths), all assessed by physical, biologic, and experimental studies.[18–22] There are evidences that laser may have the potential to offer an alternative both for prevention and treatment of established OM.[20,21,23–25] Its efficacy, however, is not fully proven although some studies do suggest stimulation of specific metabolic processes in healing wounds, thus inducing increased granulation tissue, early epithelialization, increased fibroblast proliferation and matrix synthesis, and enhanced neovascularization.[22]

Our group has recently published a study in patients above 18 years of age treated with chemotherapy and/or radiotherapy and showed that laser therapy ($\lambda = 830$ nm; 100 mW; 4 J/cm^2) is effective in OM treatment. In the laser group, the mean of OM duration was 6.8 ± 2.2 days and in the sham group was 11.5 ± 3.5 days ($P < 0.001$).[21]

We decided therefore to further explore the role of laser therapy conducting this randomized placebo-controlled trial to determine whether infrared low-intensity laser therapy (LLLT) applied every 24 hour can reduce the duration of chemotherapy-induced OM in children with cancer. We also assessed the impact of this intervention on the degree of OM on day +7 of therapy.

PATIENTS AND METHODS

This study was carried out at the Pediatric Oncology Unit (POU) of the Clinical Hospital of Porto Alegre. From October 2005 to May 2006, all children above 3 years of age and adolescents with cancer receiving chemotherapy or HSCT who developed grade 2 or greater OM were eligible for this trial. This study was approved by the Hospital Ethical Committee been approved according with National Committee in Ethic Research of Brazil register no. 05-166. All patients and/or their parents were informed about this research methodology and signed an informed consent form.

Before starting chemotherapy all patients at the POU received a routine odontologic assessment and provided with an oral care protocol. These include 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 0.12% chlorhexidine mouthrinse (free of alcohol) twice a day (after breakfast and before going to bed at night). Before every chemotherapy cycle, patients received additional reminders and instructions to reinforce compliance to the initial recommendations on tooth brushing and mouth washing. Results of blood counts at diagnosis of OM were recorded to assess the degree of myelosuppression in the arms of the study.

Laser Equipment

GaAlAs instrument by the photon laser II made by Dental Manufactory Company (DMC) Equipment (São Carlos, SP, Brazil) with a continuous 830 nm wavelength, 100 mW power was used in this trial. The treatment time (t) for each application point was given by equation t (sec) = energy (J/cm^2) × surface area (cm^2)/power (W). The energy density of 4 J/cm^2 was delivered to the mucositis lesions.

International safety procedures for laser use were followed in this study and are considered an important routine in our department. The laser was operated by a trained dentist of the POU.

Study Design

Patients were randomized by computer code generation in 2 groups: group A and group B. There was no stratification between groups.

Group A: Patients who received laser therapy: dose 4 J/cm^2.

Group B: Patients who received a placebo application/sham treatment. Only the hand piece was used, the laser was not turned on.

Patients were blind to arm allocation and as they used dark goggles and the equipment does not produce any noise and they could not tell whether the laser switch was on or off.

Laser treatment (group A) or sham treatment (group B) was applied uniformly to every OM lesions for 5 consecutive days. Laser therapy started on day 1 of admission and as was made available 7 days a week all patients entering the study could receive treatment without discontinuation. Patients remained hospitalized at least during the 7 days of the data collection and were not discharged with more than grade 2 OM. The dentist who applied the laser did not participate in the evaluation and measuring of OM. Patients received pain-control and symptomatic treatment including intravenous hydration and parenteral or enteral nutrition or support according to the severity of OM.

Definition and Scoring of OM

OM grade was scored by the same investigator, a dentist who also was blind to the randomization allocation, using the National Cancer Institute, Common Toxicity Criteria, version 2.0 scale (0 = without mucositis; 1 = painless ulcers, erythema, or mild soreness in the absence of lesions; 2 = painful erythema, edema or ulcers, but able to eat; 3 = painful erythema, edema or ulcers, requiring intravenous hydration; 4 = requires parenteral or enteral nutrition or support).[26] The grade of OM was measured at entry of study and daily until complete healing of the lesions.

Statistical Analysis

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

To compare the 2 groups, we analyzed the data on sex and disease as frequencies and percentages. Chi-square test was used to compare the distribution of patients in the solid

tumors and leukemia/lymphoma groups. Mann-Whitney test was used to compare variation in blood counts between the 2 groups. Concordance or differences in the frequency distribution between the 2 groups were tested using Student *t* test.

Multiple linear regression analysis was used to measure independent association of LLLT use and the OM duration considering sex, age, OM degree (at diagnosis and after 7 d of intervention).

A level of significance of 5% was used and data were analyzed using SPSS program, version 14.0 (SPSS).[27]

RESULTS

Twenty-one patients were included in this study according to the inclusion criteria of OM grade 2 or greater and age above 3 years; all patients completed the study. Seventeen children (81%) were males; 18 (86%) patients had leukemia/lymphoma, and 3 (14%) had solid tumors. The mean age was 8.2 ± 3.1 years. Nine patients were randomized in the laser group (group A) and 12 patients in the sham group (group B). Patients' characteristics are detailed in Table 1.

OM

OM was diagnosed at a mean of 6.6 days (5.0 to 7.5) after chemotherapy. The median of OM in grades on day 1 of diagnosis was 3 (2; 4) in the laser group and in the sham group and the mean was 3.1 (2; 4), and 3.4 (2; 4) ($P = 0.82$), respectively. None of the patients showed OM grade 1.

All patients received laser treatment (group A) or sham treatment (group B) during 5 days. Laser applications were well tolerated and there were no adverse side effects attributable to its use. The floor of the mouth (65%) and the lateral/ventral tongue (40%) were the most frequently affected sites.

There was a progressive decline on the grade of OM with complete resolution of lesions in all patients. Figure 1 illustrates the grades of OM, daily from diagnosis to resolution of the lesions.

On day 7 after OM diagnoses, 1/9 and 9/12 of patients had OM (grade 2 or greater) in the laser group and in the sham group, respectively ($P = 0.029$).

TABLE 1. Characteristics of the Patients

Variable	Laser treated (n = 9)	Sham treated (n = 12)	*P*
Age	9.0 ± 3.3	7.8 ± 3.0	0.38
Disease			
Solid tumors	1	2	0.61
Lymphomas and leukemia	6	9	
Hematopoietic stem-cell transplantation	2	1	
Leukocytes (mm^3)	600* (210; 1375)†	300 (125; 1837)	0.60
Granulocytes (mm^3)	8.9 (0; 52.4)	0 (0; 37.9)	0.65
Monocytes (mm^3)	2.8 (0; 8.5)	0 (0; 4.1)	0.34
Lymphocytes (mm^3)	21 (0; 76)	0 (0; 33)	0.14
Platelets × 10^3 (mm^3)	99 (49; 480)	94 (37; 195)	0.70

*Median.
†Percentiles 25; 75 (in parentheses).

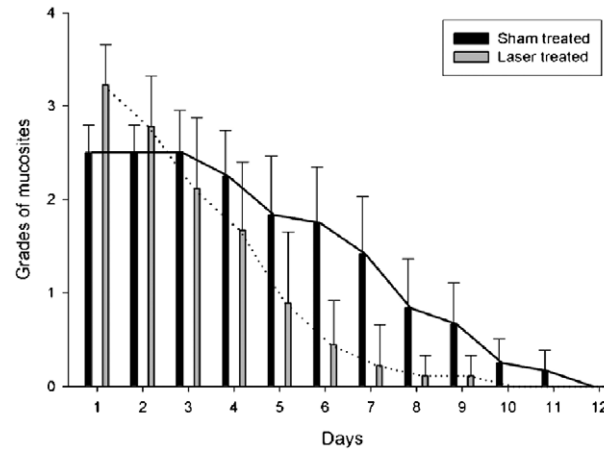

FIGURE 1. Grade of oral mucositis from start of laser or sham treatment until complete healing of the lesions.

In the group treated with laser, the mean of OM duration was 5.8 days ± 2.0 and in the sham group 8.9 days ± 2.4 ($P = 0.004$). These results mean a superiority effect of the laser treatment in 3.1 days in the OM healing process as shown in Table 2.

Multiple linear regression analysis was used to measure independent association of LLLT use and the OM duration considering sex, age, OM degree (at diagnosis and after 7 d of intervention). The laser group stayed significant ($P < 0.0001$) when compared with the placebo group.

DISCUSSION

Laser therapy has been investigated in various areas of medicine and dentistry. Results of the few published trials using the laser light to prevent or treat OM have been difficult to compare due to the lack of protocol standardization and great variations in the wavelengths tested. The studies examining the role of laser for chemotherapy-induced OM have been carried out mostly in adult cancer patients.

Most studies of LLLT in cancer patients have focused on OM prevention. Barasch et al[23] used laser prophylactically in 20 cancer patients. They received laser either in the right or the left of midline; the contralateral side was sham treated and served as a control. Patients received applications for 5 consecutive days, beginning the day after cessation of chemotherapy. OM and pain scores were significantly ($P < 0.05$) lower in the treated side.

Cowen et al[24] reported a prospective double-blind randomized trial with laser for prevention of OM in patients undergoing HSCT. They randomized 30 consecutive patients to receive prophylactic laser therapy to the oral

TABLE 2. Duration of OM

	Laser treatment (n = 9)	Sham treatment (n = 12)
OM (d)	5.8 ± 2.0	8.9 ± 2.4
Effect (d)	3.1 (95% CI, 1.1-5.2)	
P	0.004	

CI indicates confidence interval; OM, oral mucositis.

mucosa or sham therapy. Both OM index and the cumulative OM score were significantly reduced among the LLLT-treated patients.

Bensadoun et al[20] conducted a randomized multicenter trial to investigate the effectiveness of laser 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 than sham group.

Although the above studies do suggest that laser used prophylactically may reduce the severity of OM, the effect on the intensity of pain and ability to swallow, are somehow controversial. Recently, we conducted a randomized clinical trial examining the role of prophylactic laser in children with cancer at high risk of developing OM after chemotherapy. The intervention group received LLLT for 5 consecutive days; there was no evidence of benefit from the prophylactic laser applications when optimal dental and oral care is provided.[25]

As laser can decrease pain and accelerate the healing process, both in noncancer[28,29] and cancer patients [30–32] there is growing interest to study the role of laser in established chemotherapy-induced OM

Antunes et al[33] investigated the clinical effects of LLLT on prevention and reduction of severity of a conditioning regimen-induced OM in HSCT patients. In the LLLT group, 95% of patients had an OM lower or equal to grade 2, including 63% with grades 0 and 1, whereas in the controls group, 32% of patients had OM grade lower than or equal to grade 2 ($P = 0.002$).

Our own group[34] carried out a prospective pilot trial in adult cancer patients with established OM, using infrared laser, red laser, or sham treatment. Patients treated with infrared laser showed a significantly shorter duration of OM ($P = 0.0037$) and less pain both at 7 days ($P = 0.008$) and at 15 days ($P = 0.0009$) than the sham group. This study, however, had the limitation that the group allocation of patients was not randomized and the applications were made at 48 hours intervals.

The results of the present trial in children confirms the findings of our previous study in adults[21] showing that LLLT can significantly reduce the duration of chemotherapy-induced OM. The duration of OM was significantly ($P = 0.004$) shortened in patients who received laser (mean of 5.8 d) compared with control group (mean of 8.9 d) with superiority effect size of 3.1 days. In adult patients, similarly, those treated with laser had a mean duration of OM of 6.8 ± 2.2 days and in the sham group 11.5 ± 3.5 days ($P < 0.001$). The magnitude in the reduction of duration of OM in patients treated with laser was even greater in the adult study, compared with the results seen in children (4.7×3.1 d).

We designed our study to treat patients for 5 consecutive days once they entered the study; this is the time usually used in other studies.[35,36] Considering that LLLT has shown to be beneficial for OM in cancer patients, we suggest that those patients who remain with any degree of OM after the fifth day of laser therapy should carry on receiving this therapy until complete healing of the lesions.

This is the first randomized placebo-controlled study designed to confirm whether LLLT can accelerate wound healing in children with chemotherapy-induced OM. Although our study has shown evidence that LLLT in addition to oral care can decrease the duration and severity of chemotherapy-induced OM, future studies should be designed to include clinically controlled documentation of the beneficial effect in terms of pain control, narcotic administration, food intake, and length of hospital stay of patients who develop this chemotherapy complication. Our results confirm the promising results observed in adult cancer patients and should encourage pediatric oncologists to use laser therapy as first-line option for children with chemotherapy-induced OM.

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