Oral Oncology 47 (2011) 1176–1181

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

# 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

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ARTICLE INFO

*Article history:*
Received 11 May 2011
Received in revised form 23 August 2011
Accepted 24 August 2011
Available online 10 September 2011

*Keywords:*
Mucositis
Laser therapy
Side effects
Low-level laser
Head and neck cancer
Radiotherapy

SUMMARY

The purpose of this prospective study was to determine the effect of the low-level laser in the prevention and treatment of mucositis in head and neck cancer patientsA total of 70 patients with malignant neoplasms in the oral cavity or oropharynx were evaluated. The patients were randomized into two low-level laser therapy groups: Group 1 (660 nm/15 mW/3.8 J/cm$^2$/spot size 4 mm$^2$) or Group 2 (660 nm/5 mW/1.3 J/cm$^2$/spot size 4 mm$^2$) starting on the first day of radiotherapy. Oral mucositis was assessed daily and weekly using the NCI and WHO scales. Oral pain was scored daily with a visual analogue scale before laser application.The patients in Group 1 had a mean time of 13.5 days (range 6–26 days) to present mucositis grade II, while the patients in Group 2 had a mean time of 9.8 days (range 4–14 days) (both WHO and NCI $p = 0.005$). In addition, Group 2 also presented a higher mucositis grade than Group 1 with significant differences found in weeks 2 ($p = 0.019$), 3 ($p = 0.005$) and 4 ($p = 0.003$) for WHO scale and weeks 2 ($p = 0.009$) and 4 ($p = 0.013$) for NCI scale. The patients in Group 1 reported lower pain levels ($p = 0.004$). Low-level laser therapy during radiotherapy was found to be effective in controlling the intensity of mucositis and pain.



## Introduction

Oral mucositis is an acute complication resulting from antineoplastic treatment that affects patients submitted to chemotherapy in high doses and radiotherapy (RXT) in the head and neck region. Over the last 5–10 years, the prevalence of oral mucositis has increased due to new chemotherapy and RXT protocols.[1] Among patients with head and neck tumors treated with RXT, 90–97% present some degree of mucositis and generally 50% develop grade III or grade IV mucositis. In addition, 9–19% of oncological treatment interruptions are due to mucositis.[2,3]

Treatment for oral mucositis is still essentially palliative.[4] Recently, Palifermin (Kepivance®), a keratinocyte growth factor, was approved by the US Food and Drug Administration. It is used in the prevention of mucositis in patients with hematological diseases undergoing conditioning regime for bone marrow transplantation.[5–8] Nevertheless, for radio-induced oral mucositis, there is no efficient treatment.[9]

In the same way, low-level laser therapy (LLLT) has been investigated in recent studies for the prevention and treatment of oral mucositis in patients submitted to bone marrow transplantation (BMT).[10–13] The Multinational Association of Supportive Care in Cancer (MASCC) has suggested the use of laser for mucositis associated with chemotherapy but makes no specific recommendation about the use of laser for radio-induced mucositis.[1]

The laser mechanism has been described as an activation of energy production by the cytochromes in the mitochondria of oral mucosa cells, by the transmission of electrons.[14] The laser promotes rapid regeneration of the myofibroblasts originating in the fibroblasts and the growth factors of these fibroblasts maintain repair and cytotoxic protection.[15]

There are few studies about laser therapy in the prevention/treatment of mucositis caused by RXT.[16–21] Despite the different protocols used, these studies have shown that LLLT can produce some benefit to reduce the severity of oral mucositis and pain. Bensadoun et al.[16] used He–Ne laser (632.8 nm/60 mW/30 s), Arora et al.[18] also used He–Ne laser (632.8 nm/10 mW/1. 8 J/cm$^2$) daily. Zanin et al.[20] used a laser diode twice a week (660 nm/30 mW/2 J). Simões et al.[19] used LLLT (InGaAlP 660 nm/40 mW/6 J/cm$^2$) alone or associated with high power laser. However, questionable results were found by Gouvea de Lima et al.[21] that used LLLT (InGaAlP/660 nm/10 mW/spot size 4 mm$^2$) every day before radiotherapy.

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doi:10.1016/j.oraloncology.2011.08.021

The aim of this study was to evaluate the efficacy of LLLT in the prevention and treatment of radio-induced oral mucositis in patients with oral and oropharynx cancer.

## Patients and methods

### *Characterization of the study*

This study consisted of a randomized, double-blind, controlled clinical trial. A total of 70 patients, between February 2008 and December 2009, met the criteria for participation in the study. The study was approved by the Ethics Committee of Hospital A.C. Camargo, São Paulo, Brazil (no. 988/07) and all patients signed an informed consent form.

### *Inclusion criteria*

Patients with malignant neoplasms in the oral cavity and/or oropharynx were submitted to conventional three-dimensional conformal radiotherapy (RTC3D) or intensity modulated radiation therapy (IMRT) with doses in facial fields equal to or higher than 4000 cGy, either exclusively or associated with chemotherapy (cisplatin 100 mg/m$^2$ every 21 days or 50 mg/m$^2$ per week).

### *Exclusion criteria*

Patients who have previously been submitted to RXT in the head and neck or using any cytoprotector.

### *Study design*

Two randomization lists, in blocks of 6 patients, were generated by a program prepared in SAS, version 8.02. The patients were stratified by chemotherapy treatment (yes or no). Thus, a total of 70 patients were randomized by the sealed envelope method and allocated into two groups distributed in a similar manner.

Group 1 consisted of 35 patients (25 males and 10 females), age-range between 22 and 94 years (mean 56.2 ± 14.5). With regard to tumor location, 24 were located in the oral cavity (12 in the tongue) and 11 in the oropharynx. According to the proposed treatment, 14 patients were submitted to surgery and radiotherapy, 10 patients to surgery followed by radiotherapy and chemotherapy, eight patients to radiotherapy and chemotherapy and three patients received radiotherapy exclusively. Regarding chemotherapy, 15 patients were submitted to cisplatin 100 mg/m$^2$ and three patients to cisplatin 50 mg/m$^2$ (Table 1). Among the 35 patients, eight patients did not complete the study and were excluded. Two patients failed to attend the laser therapy sessions (one patient was receiving radiotherapy at another institution and another was confined to a wheelchair), one patient changed the scheme of chemotherapy from cisplatin to cetuximab, one patient died and four patients were randomized but did not begin RXT until conclusion of the study. A subsequent preliminary analysis showed statistical significance between the groups indicating that the study could be concluded.

Group 2 consisted of 35 patients (21 males and 14 females), age-range between 35 and 79 years (mean 58.1 ± 10.9). In regard to tumor location, 25 were located in the oral cavity (11 in the tongue) and 10 in the oropharynx. According to the proposed treatment, 12 patients were submitted to surgery and radiotherapy, 17 patients to surgery followed by radiotherapy and chemotherapy, five patients to radiotherapy and chemotherapy and one patient received radiotherapy exclusively. Regarding chemotherapy, 18 patients were submitted to cisplatin 100 mg/m$^2$ and four patients to cisplatin 50 mg/m$^2$ (Table 1). Eight out of 35 patients were excluded from the study, of which four patients missed the laser sessions without justification, one patient altered the treatment due to local recurrence, one patient had gastrostomy complica-

**Table 1**
Clinical features of the 70 patients evaluated in both groups.

| Variables | | | Group 1 | | Group 2 | | Total | | *p*-Value |
|---|---|---|---|---|---|---|---|---|---|
| | | | *N* | % | *N* | % | *N* | % | |
| Gender | Male | | 25 | 71.4 | 21 | 60 | 46 | 65.7 | 0.314 |
| | Female | | 10 | 28.6 | 14 | 40 | 24 | 34.3 | |
| Age (years) | Range | | 22–94 | | 35–79 | | 22–94 | | 0.541 |
| | Mean ± SD | | 55.2 ± 4.5 | | 58.1 ± 10.1 | | 57.1 ± 12.8 | | |
| Tumor location | Mouth | Tongue | 12 | 34.3 | 11 | 31.4 | 23 | 32.9 | 0.990 |
| | | Buccal | 3 | 8.6 | 4 | 11.4 | 7 | 10.0 | |
| | | Palate | 2 | 5.7 | 4 | 11.4 | 6 | 8.6 | |
| | | Trigone | 1 | 2.9 | 1 | 2.9 | 2 | 2.9 | |
| | | Gingiva | 1 | 2.9 | 1 | 2.9 | 2 | 2.9 | |
| | | Floor | 4 | 11.4 | 4 | 11.4 | 8 | 11.4 | |
| | | Lip | 1 | 2.9 | 0 | 0.0 | 1 | 1.4 | |
| | Oropharynx | | 11 | 31.4 | 10 | 28.6 | 21 | 30 | |
| Clinical stage | I | | 4 | 11.4 | 0 | 0 | 4 | 5.7 | 0.140 |
| | II | | 6 | 17.1 | 6 | 17.1 | 12 | 17.1 | |
| | III | | 11 | 31.4 | 10 | 28.6 | 21 | 30.0 | |
| | IV | | 14 | 40.0 | 19 | 54.3 | 33 | 47.1 | |
| Treatment | Sur + RxT | | 14 | 40.0 | 12 | 34.3 | 26 | 37.1 | 0.300 |
| | Sur + RxT + CH | | 10 | 28.6 | 17 | 48.6 | 27 | 38.6 | |
| | RxT + CH | | 8 | 22.9 | 5 | 14.3 | 13 | 18.6 | |
| | RxT | | 3 | 8.6 | 1 | 2.9 | 4 | 5.7 | |
| RxT type | 2D | | 7 | 20.0 | 3 | 8.6 | 10 | 14.3 | 0.308 |
| | 3D | | 15 | 42.9 | 20 | 57.1 | 35 | 50.0 | |
| | IMRT | | 13 | 37.1 | 12 | 43.3 | 25 | 35.7 | |
| RxT dose (GY) | 60–64 | | 14 | 51.8 | 18 | 66.6 | 32 | 59.3 | 0.450 |
| | 65–72 | | 13 | 48.2 | 9 | 33.4 | 22 | 40.7 | |
| CH dose (mg/m$^2$) | 50 | | 03 | 16.7 | 05 | 22.7 | 08 | 20.0 | 0.709 |
| | 100 | | 15 | 83.3 | 17 | 77.3 | 32 | 80.0 | |

SD – standard deviation; CH – chemotherapy; RxT – radiotherapy; Sur – surgery.

tions, one patient died and another patient was randomized but did not begin RXT until conclusion of the study.

*Prophylactic laser applications*

In both groups, the appliance used was a gallium aluminum–arsenate (InGaAlP) diode laser (Twin laser – MMOptics®, MMOptics Ltda., São Carlos, São Paulo, Brazil). For Group 1, the laser illumination consisted of a continuous 660 nm wavelength, power 15 mW, spot size 4 $mm^2$ and energy density delivered to the oral mucosa was 3.8 $J/cm^2$ For Group 2, the laser illumination consisted of a continuous wavelength 660 nm, power 5 mW, spot size 4 $mm^2$ and 1.3 $J/cm^2$ of energy density delivered to the oral mucosa. The device and light color were identical for both groups.

In both groups, each anatomic site was illuminated for 10 s. All applications were performed by a single professional, blinded to the laser groups. The anatomical areas of the oral mucosa were irradiated according to the procedure described by Jaguar et al.[13] The tumor area (or previous tumor area) was excluded from the field of laser illumination.

In both groups, the applications were realized daily, five consecutive days per week, starting on the first day of RXT (always before the radiation sessions). All patients that participated in the study received preventive LLLT in the oral normal mucosa. The patients who developed grade II mucositis (in both groups) stopped the prophylactic protocol and began curative laser therapy (performed with another device) that consisted of a continuous 660 nm wavelength, power 15 mW, spot size 4 $mm^2$ and energy density of 3.8 $J/cm^2$ delivered in each ulcerated area of oral mucosa. These patients continued to be followed-up and evaluated in regard to the degree of mucositis and pain until the end of RXT treatment.

All patients underwent oral care protocol before starting RXT. The oral care protocol included oral examination, preventive dental treatment, instructions for oral care during radiation therapy and prescription mouthwashes and fluoride (if dentate).

*Oral mucositis evaluation*

Oral mucositis was evaluated on a daily and weekly basis in accordance with the classification criteria of the National Cancer Institute (NCI) and the World Health Organization (WHO).[22]

*Oral pain evaluation*

In relation to oral pain, the patients were analyzed up to the 30th day of RXT and the pain was evaluated subjectively according to a visual analog scale (VAS), in which "0" is the absence of pain and "10" is maximum pain. The patients were instructed to attribute a score to their degree of pain in oral mucositis.

*Statistical analysis*

The Student's-*t* test was used for the comparison of age between the two groups. The Chi-Square test was used to verify association between the variables gender, tumor location, Group 1 or Group 2, type and dose of RXT. The ordinal logistic regression model was used to verify whether there was difference in staging between the two groups, as well as to compare the WHO and NCI degree of mucositis between the two groups. In the comparison of pain intensity between the two groups, the area under the curve of pain scores of the first 30 days of evaluation was calculated. The areas under the curve were compared by means of the Student's-*t* test.

The statistical software programs used in the analyses were XLSTAT 2009 and Minitab 14.

## Results

*Daily evaluation of mucositis*

According to the WHO scale, the patients in Group 1 had a mean time of 13.5 days (range 6–26 days) to present mucositis grade II, and the patients in Group 2 had a mean time of 9.8 days (range 4–14 days) ($p = 0.005$). Similar data were also observed with the NCI classification (Table 2).

For development of mucositis grade III (WHO scale), the patients in Group 1 and in Group 2 had a mean time of 23.6 days (range 11–31 days) and 17.1 days (range 10–31 days) ($p = 0.014$), respectively. According to NCI scale, the patients had a mean time of 19.1 days (range 11–32 days) and 17.2 days (range 8–33 days) ($p = 0.498$), respectively (Table 2).

*Weekly evaluation of mucositis*

In the weekly comparison in accordance with the WHO scale, Group 2 presented a significantly higher mean of mucositis grade than Group 1 in weeks 2 ($p = 0.019$), 3 ($p = 0.005$) and 4 ($p = 0.003$) (Table 3) (Fig. 1A). In addition, only one patient in Group 1 presented mucositis grade IV, which occurred in week 5 of RXT. However, in Group 2, six patients (22.2%) had mucositis grade IV.

**Table 2**
Mean and median of days for the patients develop mucositis grades II and III.

| Mucositis | Scales | Groups | *N* | Mean ± SD (range) | Median | *p*-Value |
|---|---|---|---|---|---|---|
| Grade II | WHO | 1 | 25 | 13.5 ± 5.7 (6–26) | 11.0 | 0.005* |
| | | 2 | 27 | 9.8 ± 2.6 (4–14) | 9.0 | |
| | NCI | 1 | 25 | 13.5 ± 5.7 (6–26) | 11.0 | 0.005* |
| | | 2 | 27 | 9.8 ± 2.6 (4–15) | 9.0 | |
| Grade III | WHO | 1 | 13 | 23.6 ± 7.2 (11–31) | 26.0 | 0.014* |
| | | 2 | 17 | 17.1 ± 6.0 (10–31) | 14.0 | |
| | NCI | 1 | 17 | 19.1 ± 6.9 (11–32) | 18.0 | 0.498 |
| | | 2 | 21 | 17.5 ± 7.5 (8–33) | 15.0 | |

SD – standard deviation.
* Means statistically significant.

**Table 3**
Mean grade of mucositis per week, during 7 weeks of treatment according to WHO and NCI.

| Week(s) | *N* (patients) | Group 1 | | Group 2 | | *p*-Value (WHO) | *p*-Value (NCI) |
|---|---|---|---|---|---|---|---|
| | | Mean (WHO) | Mean (NCI) | Mean (WHO) | Mean (NCI) | | |
| 1 | 27 | 0.00 ± 0.00 | 0.00 ± 000 | 0.11 ± 0.42 | 0.11 ± 0.42 | – | – |
| 2 | 27 | 0.78 ± 0.93 | 0.78 ± 0.93 | 1.41 ± 0.93 | 1.56 ± 1.09 | 0.019 | 0.009 |
| 3 | 27 | 1.59 ± 0.97 | 1.74 ± 1.10 | 2.30 ± 0.47 | 2.33 ± 0.48 | 0.005 | NS |
| 4 | 27 | 1.52 ± 0.85 | 1.63 ± 0.97 | 2.30 ± 0.87 | 2.33 ± 0.88 | 0.003 | 0.013 |
| 5 | 27 | 1.85 ± 0.82 | 1.93 ± 0.87 | 2.19 ± 0.88 | 2.22 ± 0.89 | NS | NS |
| 6 | 27 | 2.15 ± 0.72 | 2.15 ± 0.77 | 2.19 ± 0.96 | 2.26 ± 0.98 | NS | NS |
| 7 | 17 | 2.35 ± 0.61 | 2.44 ± 0.62 | 2.00 ± 0.79 | 2.12 ± 0.86 | NS | NS |

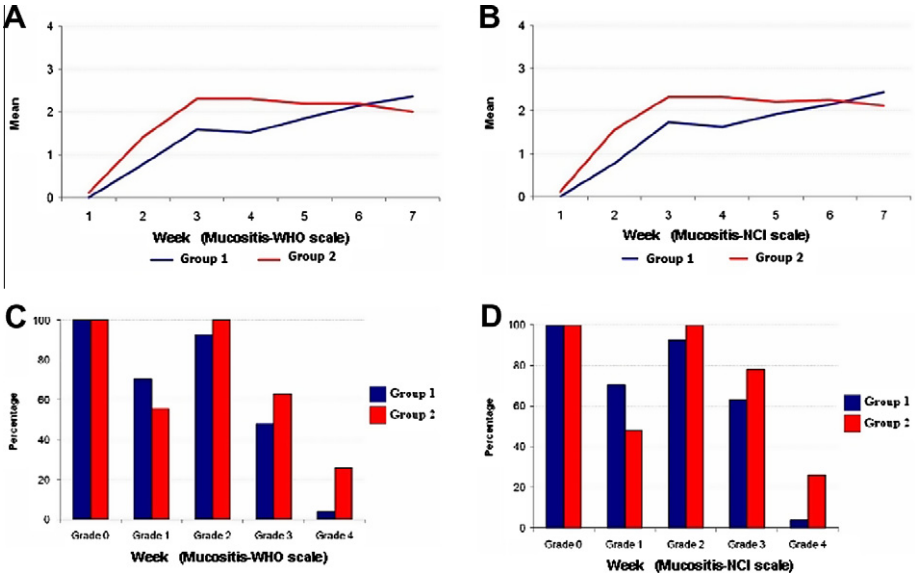


**Figure 1** Mean grade of mucositis evaluated weekly in both Groups 1 and 2 according to WHO scale (A) and NCI scale (B). Evaluation of the severity of oral mucositis between Groups 1 and 2 according to WHO (C) and NCI scales (D).

Differences were also found between the two groups considering NCI mucositis in weeks 2 ($p = 0.009$) and 4 ($p = 0.013$). The grade of mucositis in Group 2 was higher than it was in Group 1 (Table 3) (Fig. 1B).

The percentage of patients that presented grade I was higher in Group 1 in the two classifications, for grades II, III and IV the opposite occurred. The NCI classification had a higher percentage of grade III than the WHO classification (Fig. 1C and D).

## Pain

Up to the fifth day of evaluation, no patient in Group 1 complained of oral pain, but in Group 2 two patients reported pain. The highest pain scores occurred during the third week in both groups (Fig. 2). Importantly, the mean intensity of pain was always higher for Group 2 ($p = 0.004$).

## Discussion

Radio-induced oral mucositis is the main acute effect in patients undergoing RXT for treatment of head and neck tumors. At present, there is no therapy capable of completely preventing mucositis and LLLT is a new therapeutic option for its management. Considering mucositis related to BMT or to high doses of chemotherapy, laser therapy has been effective in the prevention and healing of lesions.[10–13] In addition, some studies[16–18] have also confirmed its efficacy in diminishing the severity and delaying the manifestation of radio-induced mucositis.

The first study that evaluated the LLLT in radio-induced oral mucositis was conducted by Bensadoun et al.[16] where the patients were divided into two groups receiving laser or sham light. All applications were performed by the same operator, but this person did not participate in the evaluation and scoring of mucositis. Otherwise, the present study consisted of a randomized, double-blinded clinical trial to evaluate the effects of the LLLT in which a single operator performed both devices that emitted light with similar color. Group 2 consisted of a continuous wavelength 660 nm, power 5 mW and 1.3 J/cm$^2$ of energy density delivered in each point of the oral mucosa. According to the manufacture (MMOptics), this illumination has minimal biological effects. Group 1 consisted of a continuous 660 nm wavelength, power 15 mW with 3.8 J/cm$^2$energy density delivered in each point of the oral mucosa. Thus, this study was the first to compare the effects of laser therapy and light with no or minimal effects in cells. In addition, for ethical reasons, independent of Groups 1 or 2, if the patient presented grade II mucositis, a curative laser therapy (wavelength of 660 nm, 15 mW potency, and energy density of 3.8 J/cm$^2$ per point) was started according to the protocol of the Stomatology Department at Hospital A.C. Camargo. However, the patient continued to be followed in their original group.

In the present study, the patients were evaluated on a daily and weekly basis. In our opinion, the daily evaluation was important to show the precise development of ulcerated mucositis (grade II) from the oral normal mucosa. Thus, Group 1 presented oral ulcer

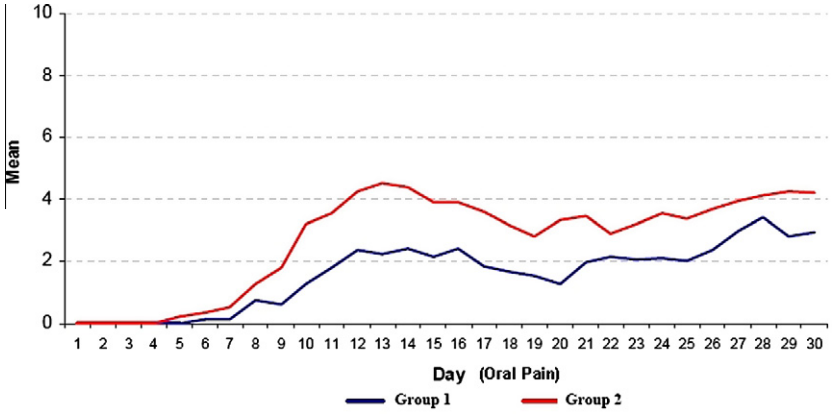


**Figure 2** Mean score of oral pain evaluated daily in both Groups 1 and 2.

lesions (mean of 13 days after the beginning of RXT) approximately 4 days later than Group 2, according to both WHO and NCI scales. Arora et al.[18] also evaluated their patients on a daily basis. However, the authors presented their results scored in weekly evaluation as in the Bensadoun study.

In the current study, considering the weekly basis, Group 1 developed lower mucositis grades than Group 2, with statistical significance between the second to fourth weeks (according to both WHO and NCI scales). In the adjacent weeks, both Groups 1 and 2 presented similar mucositis grades. These data can clearly be observed in Fig. 1A and B. On the other hand, Bensadoun et al.[16] found statistical significance in the fourth to seventh and Arora et al.[18] in the second to seventh weeks. In addition, we investigated the probable explanations for this difference. First, as was commented above, when the patients presented grade II mucositis, independent of the group, they received curative laser therapy with the same specifications in both groups. Another fact, RXT interruption occurred in six patients in Group 2 against one in Group 1 (due to mucositis) and consequently, the mucositis intensity ameliorated in these patients.

Arora et al.[18] also showed that all patients independent of the group presented ulcerated oral mucositis (grade II mucositis). In addition, four patients (30.8%) in the control group developed mucositis grade IV, whereas in the laser group, no patient had this grade. Similarly, in our study only two patients in Group 1 did not present ulcerated mucositis. Nevertheless, one (3.7%) patient in Group 1 developed Grade IV oral mucositis and six (22.2%) patients in Group 2 had their treatment interrupted due to grade IV mucositis. Different than in the study of Bensadoun et al.[16] no patient presented oral mucositis grade IV, neither in Group 1 nor Group 2. A possible explanation could be that in the Bensadoun study, nine out of 30 patients (five in placebo group and four in laser group) had primary tumors located in the hypopharynx; such patients usually present a lower incidence of oral mucositis. Likewise, Gouvea de Lima et al.[21] presented 35 out of 74 patients (18 in placebo group and 17 in laser group) with primary tumors located in different sites of the oral cavity and oropharynx. This could explain the low rate of mucositis grade III–IV. Despite the significant difference from week 1, Zanin et al.[20] had 30 out of 72 patients in their study (16 in control group and 14 in laser group) and no patient presented grade IV mucositis. Arora et al.[18] analyzed only patients with oral cavity tumors and in our study we randomized patients with malignant neoplasms in the oral cavity and/or oropharynx.

With regard to pain, the present study showed a significant reduction in pain scores. Patients were evaluated on a daily basis, always before the application of laser therapy. On average, Group 1 always presented lower pain scores than Group 2. Bensadoun et al.[16] evaluated the patients once a week by means of a modified visual analog scale. The highest pain scores were found in the fifth week of treatment, and the group treated with laser always presented a lower mean than the group treated with sham light. Arun Maya et al.[17] had their patients evaluated by a professional who did not know which group was having the laser treatment. The pain scores were also significantly lower for the group treated with laser ($2.6 \pm 0.64$) than for the control group ($6.68 \pm 1.44$). Arora et al.[18] examined the patients in the morning before the RXT sessions through a numerical scale and consumption of analgesics, according to the WHO analgesic scale. Although a significant reduction of pain scores was observed in the laser group, no significant difference was found, between the groups, in regard to the consumption of analgesics.

In summary, LLLT appears to present promising results, both in control of the intensity of mucositis and in the pain related to the mucositis. However, further studies are necessary to define the dose, application time and number of sessions in patients submitted to oncological treatments.

## Conflict of interest statement

None declared.

## Acknowledgments

The authors would like to thank FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) for financial support.

The authors would also like to thank the Professor Todd Price for paper English revision.

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