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ORIGINAL ARTICLE

Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation

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AIM: To evaluate the clinical effects of laser therapy on the prevention and reduction of oral mucositis in patients who underwent hematopoietic stem cell transplantation (HSCT).

PATIENTS AND METHODS: From January 2003 to September 2004, 24 patients received prophylactic laser therapy (L+ group). The applications started from the beginning of the conditioning regimen up to day +2. The oral assessment was performed daily until day +30. This group was compared with historical controls, namely 25 patients, who did not receive laser therapy (L− group).

RESULTS: All patients developed some grade of mucositis. However, the L− group presented initial mucositis by 4.36 days, whereas the L+ group presented it in 6.12 days ($P = 0.01$). The maximum mucositis occurred between day +2 and day +6 with healing by day +25 in the L− group and between day +2 and day +7 with healing by day +14 for the L+ group ($P = 0.84$). Laser therapy also reduced the time of oral pain from 5.64 to 2.45 days ($P = 0.04$), and decreased the consumption of morphine ($P = 0.07$).

CONCLUSION: This study suggests that laser therapy can be useful in oral mucositis to HSCT patients and improve the patient's quality of life. However, controlled randomized trials should be performed to confirm the real efficacy of laser therapy.

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Keywords: oral mucositis; laser; side effects; hematopoietic stem cell transplantation

Introduction

Intensive cancer therapy typically affects malignant and normal cells with high replicative rates, such as oral epithelial basal cells (Chiappelli, 2005). Oral mucositis is a frequent complication in patients undergoing hematopoietic stem cell transplantation (HSCT) and presents as erythema, ulceration, bleeding, and edema along with pain (Duncan and Grant, 2003; Epstein and Schubert, 2003; Sonis *et al*, 2004). The incidence and severity of oral mucositis depend on chemotherapy regimen and on treatment modality (Rubenstein *et al*, 2004). Conditioning regimens that include high-dose chemotherapy with total body irradiation (TBI) are associated with the highest rates of mucositis (Sonis *et al*, 2004). In addition, oral mucositis incidence ranges from 75% to 85% in HSCT patients and it has been reported as one of the most debilitating side effects (Bellm *et al*, 2000; Sonis *et al*, 2004).

Oral mucositis can also cause severe sequelae such as local and systemic infections and decrease patient's willingness to continue treatment (Migliorati *et al*, 2006). Deglutition and mastication may be intolerable, requiring parenteral nutrition and opioid analgesics in approximately 87% and 80% of HSCT patients, respectively (McGuire *et al*, 1993; Sonis *et al*, 2004).

Several therapies such as prostaglandin E_2 (Labar *et al*, 1993), vitamin E (Borek, 2004), cryotherapy (Rocke *et al*, 1993; Yokomizo *et al*, 2004), chlorhexidine digluconate (Dodd *et al*, 2000), benzydamine hydrochloride (Epstein *et al*, 2001), and palifermin (Spielberger *et al*, 2004; Keefe *et al*, 2006; Stiff *et al*, 2006) have been used to target against oral mucositis.

Recently, the recombinant keratinocyte growth factor Palifermin (Kepivance™, Amgen Manufacturing Limited, Thousand Oaks, CA, USA), a cytoprotective agent was approved by the US Food and Drug Administration and other regulatory authorities around the world because of its ability to promote thickening of the oral epithelium. It found use in the prevention of oral mucositis in patients receiving conditioning regimens for HSCT in the treatment of hematologic malignancies (Danilenko, 1999; Spielberger *et al*, 2004; Awada *et al*, 2005; Radtke *et al*, 2005; Keefe *et al*, 2006; Scully *et al*, 2006; Stiff *et al*, 2006).

Additional to these therapies, a few publications have documented the evidence that low-energy laser (LEL) therapy may be useful in decreasing the severity of mucositis and consequently its pain (Barasch *et al*, 1995;

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Cowen *et al*, 1997; Bensadoun *et al*, 1999; Migliorati *et al*, 2001; Wong and Wilder-Smith, 2002). These studies have attributed the enhancement of wound healing and pain relief potential of LEL to microscopic findings as increased cell division and modification of nerve conduction via the release of endorphins and enkephalins.

The aim of this study was to investigate the clinical effects of LEL therapy on prevention and reduction of conditioning-induced oral mucositis for HSCT patients.

Patients and methods

Patient characteristics
This study consisted of two groups.

Group L− (without laser therapy)
It was formed by a historical control group ($n = 25$ patients) treated between 1999 and 2000, who did not receive LEL radiation. (During this time, laser therapy was not performed as part of the HSCT protocol at our institution.) The clinical data were collected from the files of A. C. Camargo Cancer Hospital, São Paulo, Brazil. One experienced clinician revised the information in the files from the beginning of the conditioning regimen to 30 days after stem cell transplantation (day +30).

In this group, 23 out of 25 patients received the autologous, while 2 out of 25 received the allogenic transplant. The malignancies were eight non-Hodgkin's lymphoma, seven Hodgkin's lymphoma, three testicular cancers, and seven multiple myeloma. None of the patients received TBI (Table 1). The two patients who underwent allogenic transplant had non-Hodgkin's lymphoma.

Group L+ (with laser therapy)
It consisted of an experimental group ($n = 24$ patients) treated between January 2003 and September 2004 that received prophylactic laser (part of HSCT protocol). The oral examination was performed by one experienced clinician daily, from the beginning of the conditioning regimen to 30 days after stem cell transplantation (day +30).

In this group, 21 out of 24 patients received the autologous while 3 out of 24 received the allogenic transplant. The malignancies were four non-Hodgkin's lymphoma, seven Hodgkin's lymphoma, six testicular cancers, and seven multiple myeloma. Six patients received TBI, three multiple myeloma and three Hodgkin's lymphoma (Table 1). The three patients who underwent the allogenic transplant had non-Hodgkin's lymphoma.

Table 1 Patients characteristics in groups L− and L+

Variables	*Total*	*L− (n)*	*L+ (n)*	*P*-value
Patients	49	25	24	
Age				
Range		17–62	17–56	0.32
Mean (±)		37.4 (13.0)	33.8 (12.6)	
Median		34	32	
Gender				
Female	17	9 (52.9%)	8 (47.1)	0.84
Male	32	16 (50.0%)	16 (50.0%)	
Type of transplant				
Autologous	44	23 (52.2%)	21 (47.7%)	0.66
Allogenic	5	2 (40.0%)	3 (60.0%)	
Malignancy				
Non-Hodgkin's lymphoma	12	8 (66.7%)	4 (33.3%)	0.51
Hodgkin's lymphoma	14	7 (50.0%)	7 (50.0%)	
Multiple myeloma	14	7 (50.0%)	7 (50.0%)	
Testicular cancer	9	3 (33.3%)	6 (66.7%)	
Conditioning regimen				
Chemotherapy	43	25 (58.2%)	18 (41.9%)	0.01
Chemotherapy + TBI	6	0 (0.0%)	6 (100.0%)	

L−, without laser therapy; L+, with laser therapy; TBI, total body irradiation.

Exclusion criteria
We excluded the patients treated between 2001 and 2002 because the standard protocol of prophylactic laser therapy for oral mucositis had not been established then in our institution.

Preparative regimens
In both groups (L− and L+) non-Hodgkin's lymphoma and Hodgkin's lymphoma patients (autologous or allogenic transplant) received carmustine, cyclophosphamide, and etoposide; testicular cancer patients received ifosfamide, carboplatin, and taxol; and, multiple myeloma patients received melphalan. The specific dosage for each disease, and transplant type are observed in Table 2.

In the L+ group, three myeloma multiple and three Hodgkin's lymphoma patients received TBI (2 Gy daily for 3 days). All autologous patients received an infusion of 300 mcg day^{-1} granulocyte colony-stimulating factor on day +1 and followed daily until adequate hematologic recovery (neutrophil counts >1000 cells mm^{-3}) as part of the HSCT protocol.

The oral care protocol consisted of 0.12% chlorhexidine digluconate rinse three times a day, oral cryotherapy with flavored ice pops (5 min before initiating chemotherapy and continued for about 30 min) and a lip protector.

Mucositis assessment
The severity of oral mucositis was scored according to WHO (Parulekar *et al*, 1998): grade 0 (none), grade I (oral soreness, erythema), grade II (oral erythema, ulcers, solid and liquid diet tolerated), grade III (oral ulcers, liquid diet only), and grade IV (oral alimentation impossible). Oral pain was evaluated by the administration of narcotics (morphine) and the time of parenteral nutrition. The usual dosage range of morphine sulfate was 10–30 mg every 4 h as needed.

Prophylactic laser treatment
Patients received gallium aluminum arsenate (GaAlAs) diode laser (Twin laser- MM Optics®, MM Optics Ltda., São Carlos, São Paulo, Brazil) therapy on four anatomic sites of the oral mucosa (the right- and left-hand side of the cheeks; lower and upper labial mucosa, ventral and lateral tongue, and floor of the mouth), from

Table 2 Preparative regimens according to the malignancies and transplant type

	Drugs						
No./malignancy	*Carmustine (mg m^{-2})*	*Cyclophosphamide (mg m^{-2})*	*Etoposide (mg m^{-2})*	*Melphalan (mg m^{-2})*	*Taxol (mg m^{-2})*	*Ifosfamide (g m^{-2})*	*Carboplatin (mg m^{-2})*
14/HL and 7/NHL (autologous transplant)	day −8 to day −6 (100)	day −5 to day −2 (900)	day −8 to day −6 (400)	–	–	–	–
5/NHL (allogenic transplant)	day −6 to day −3 (112)	day −6 to day −6 (750)	day −6 to day −3 (200)	–	–	–	–
14/multiple myeloma	–	–	–	day −1 (200)	–	–	–
9/testicular cancer	–	–	–	–	day −4 and day −3 (250)	day −7 to day −5 (3)	day −7 to day −5 (400)

HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; –, drug not used.

the beginning of the conditioning regimen to the second day after stem cell transplantation (day +2). The laser illumination consisted of a continuous 660 nm wavelength, power 10 mW and the energy density delivered to the oral mucosa was 2,5 J cm^{-2}. Each anatomic site was illuminated for 10 s per point. During the applications, the patients wore wavelength-specific dark glasses to avoid retinal exposure to laser light.

Statistical analysis

The association with categorical variables and laser using contingency tables was verified by chi-square frequency tests and in case even one expected frequency was observed in 2 × 2 tables, the Fisher exact test was used. For continuous variables the nonparametric Mann–Whitney *U*-test was adopted. The 5% level of significance was considered for all tests.

Results

The laser therapy applications were well tolerated for L+ group and no side effects were observed. All patients, both in the L+ and in the L− group, showed some grade of oral mucositis. However, the patient percentage that developed mucositis grade II, grade III and grade IV was lower in the L+ group, but it was not statistically significant ($P = 0.12$; Figure 1).

Considering grade I mucositis, patients in the L− group showed the first oral clinical changes between day −5 and day +2, with a mean time of 4.36 days after the conditioning regimen. On the other hand, patients in the L+ group presented grade I mucositis between day −3 and day +5, with a mean time of 6.12 days ($P = 0.01$).

The highest score of mucositis (grade IV), in the L− group, started between day +2 and day +6 with healing by day +8 and day +25, with a mean time of grade IV mucositis around 3 days. The patients in the L+ group presented between day +2 and day +7 with healing by day +8 and day +14, with a mean time of 3 days ($P = 0.84$).

In the L− group, 15 (60.0%) patients presented pain *vs* 9 (33.33%) patients in the L+ group ($P = 0.06$; Figure 2). Considering the time of oral pain, the patients in the L− group showed pain from day +1 to day +25, with a mean time of 5.64 days, whereas, the patients in the L+ group presented pain from day +1 to day +14, with a mean time of 2.45 days ($P = 0.04$; Figure 2).

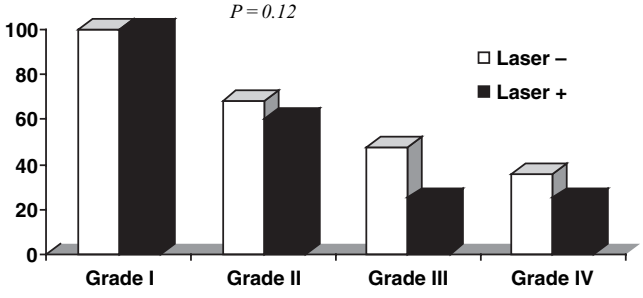

Figure 1 Evaluation of severity of oral mucositis (Parulekar *et al*, 1998) between the groups Laser− and Laser+

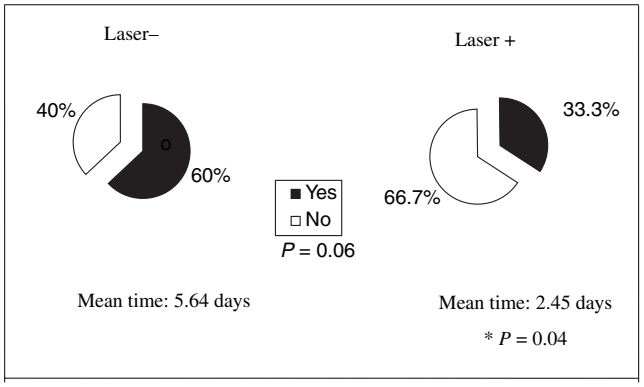

Figure 2 Evaluation of the incidence and prevalence of pain between the groups Laser– and Laser+

Morphine was required in 10 (40.0%) patients from the L– group *vs* 4 (16.67%) patients from the L+ group ($P = 0.07$). In the L– group, the patients used morphine during a mean time of 8.2 days *vs* 8.5 days for the L+ group ($P = 0.91$).

Parenteral nutrition was required in 9 (36.0%) patients from the L– group *vs* 8 (33.30%) patients from the L+ group ($P = 0.84$). Considering the time of parenteral nutrition, in the L– group, the patients used this procedure during a mean time of 3 days *vs* 2.8 days in the L+ group ($P = 0.84$).

Discussion

Oral mucositis is a common and serious complication of HSCT conditioning regimens. Many agents have been tested for prevention and treatment of these lesions. In the multi-centre, double-blind, phase III study of Spielberger *et al* (2004), 212 patients who underwent the autologous transplant were randomized to receive 60 mcg kg^{-1} day^{-1} of Palifermin or placebo, for 6 days. The authors showed that in patients who experienced grade III or IV oral mucositis, the average duration of this grade of mucositis in the Palifermin group was 6 days compared with 9 days in the placebo group ($P < 0.001$), and the overall incidence of these grades was also significantly reduced in the Palifermin group (Palifermin = 63% *vs* placebo = 98%, $P < 0.001$). The reduction in patient-reported soreness of the mouth and throat, the use of opioid analgesics, and the incidence of the use of total parenteral nutrition were also associated with the use of palifermin (Keefe *et al*, 2006; Stiff *et al*, 2006). Further, benzydamine hydrochloride has also shown significant benefit in reducing the intensity and duration of mucosal damage in radiation patients because of its capacity to inhibit tumor necrosis factor (Sironi *et al*, 1997; Epstein *et al*, 2001).

In a review on oral mucositis Scully *et al* (2006) showed a significant effect of Palifermin (Kepivance®), benzydamine, cryotheraphy and other therapies on ameliorating mucositis. Considering that mucositis can affect all of the oro-esophageal and gastrointestinal mucosae, it must be stressed that these therapies could be used in association with laser therapy, inasmuch as laser therapy only acts on oral and anal mucosae.

In this context, our study was designed to evaluate the impact of prophylactic laser therapy in the management of oral mucositis. Although the precise laser mechanisms that promote wound healing, reduce inflammation and pain have not yet been elucidated, some explanations have been reported. Karu (1989) showed that the laser energy is absorbed at the mitochondria by cytochromes, causing transmission of electrons and leading to an enhancement of protein synthesis which may be capable of promoting wound healing. It has also been demonstrated that LEL irradiation results in a rapid generation of myofibroblasts from fibroblasts and that fibroblast growth factors can develop epithelial repair and cytokine protection (Pourreau-Schneider *et al*, 1990). In addition, the LEL anti-inflammatory effect seems to be related to a reduction in oxygen free radicals during chemotherapy and radiotherapy (Gate *et al*, 1999), and the analgesic action may be explained by a modulation of nociception (Franquin, 1993).

Genot and Klastersky (2005) reviewed the literature about the LEL therapy for the prevention of oral mucositis in patients undergoing HSCT conditioning regimens and found only three studies – Barasch *et al* (1995), who treated 20 patients prophylactically with LEL irradiation to either the right or left oral mucosa (the contralateral side served as a control); Cowen *et al* (1997), who conducted a prospective and double-blind study of laser therapy in 30 patients undergoing autologous HSCT; and Migliorati *et al* (2001), who compared 11 patients receiving high-dose chemotherapy for various hematologic malignancies, with or without HSCT. In this report, an experimental group (n = 24 patients) was compared with a historical control (n = 25 patients). In both groups, most patients underwent autologous HSCT (23/25 in the L– group and 21/24 in the L+ group). Despite the heterogeneity of this study design, it was possible because of the efficient file system at the Cancer Hospital A.C. Camargo.

There are different approaches regarding the period of laser applications in HSCT, as well as the energy density delivered. Barasch *et al* (1995) performed laser applications from day − 1 to day +3 and the energy density delivered was 1.0 J cm^{-2}; Cowen *et al* (1997) from day −5 to day −1 with 1.5 J cm^{-2} and Migliorati *et al* (2001) from day −5 to day +5 with 1.5 J cm^{-2}, while in the present report, from the beginning of the conditioning regimen to day +2 with 2.5 J cm^{-2}. Besides, while the energy density might be the only parameter of the dose-dependent treatment (Woodruff *et al*, 2004), the optimal density and irradiation time of laser applications still need to be defined. In all these studies, including ours, the laser therapy applications were well tolerated and side effects were not observed.

In the current study, the incidence of oral mucositis was identical (100%) in the L– group and L+ group, similar to most reports (Barasch *et al*, 1995; Cowen *et al*, 1997). However, Wong and Wilder-Smith (2002) presented different data, where the prophylactic laser effect on the oral mucosa of 15 patients receiving

5-fluorouracil continuous infusion for various hematologic malignancies, without HSCT, who had developed an episode of prior chemotherapy-induced grade III–IV mucositis, was examined. These authors showed a decreased incidence of mucositis with LEL therapy, where 11 out of 15 patients did not develop mucositis, 3 out of 15 patients showed grade I–II mucositis, and 1 out of 15 experienced grade III–IV mucositis. The higher toxicity used in HSCT-conditioning regimens is one possible explanation for this difference in incidence. In addition, conditioning regimens that include high-dose chemotherapy with TBI are associated with the highest rates of mucositis (Sonis *et al*, 2004). In our sample six patients in the L+ group received this treatment and none received this more aggressive treatment in the L− group.

In this study, the severity of oral mucositis was scored according to WHO (Parulekar *et al*, 1998). This method mixes tissue damage and function; however, it is easy and is recommended to support patient care in oncology treatment (Epstein and Schubert, 2003). Besides, while our data did not present significant findings concerning the incidence of oral mucositis, they suggest that laser therapy may reduce the peak severity of HSCT-induced oral mucositis as previously reported by other studies (Barasch *et al*, 1995; Cowen *et al*, 1997; Migliorati *et al*, 2001). We noted in the L− group that 21 (84.0%) patients developed grade III–IV oral mucositis whereas in the L+ group 12 (50.0%) patients presented grade III–IV oral mucositis ($P = 0.12$). Probably, if the number of patients was higher, this result would be statistically significant.

Grade I mucositis on the laser-treated side of the oral cavity was noted 7–10 days after the initiation of cytotoxic therapy (Barasch *et al*, 1995). In the present study, grade I mucositis in the L− group was noted 4.36 days after initiation of the conditioning regimen and in the L+ group after 6.12 days ($P = 0.01$). Regarding the highest score of oral mucositis, it has been reported to vary between day +7 and day +11 (13–17 days after the initiation of cytotoxic therapy) with healing by day +20 without the LEL therapy (Schubert *et al*, 1994). We observed maximum oral mucositis between day +2 and day +6 with healing by day +25 for the L− group and between day +2 and day +7 with healing by day +14 for the L+ group. Consequently, severe oral mucositis in patients without LEL therapy probably takes more time to heal, which significantly affect the patients' quality of life, due to the presence of neutropenia, mucositis predisposes to septicemia, bacteremia, and fungemia. In addition, we observed that a 1-point increase in oral mucositis score was associated with a significant increase in oral pain.

From the patient's perspective, acute oral pain is the most debilitating effect caused by mucositis, because it interferes in the ability to eat, swallow and speak, and results in an increase in the number of days of morphine administration and parenteral nutrition. Cowen *et al* (1997) showed a statistically significant reduction in the time of oral pain in patients who underwent LEL therapy, where the mean time of pain was 20.3 days for the L− patients and 12.7 days for the L+ patients. Our results are in agreement with this report, which showed a mean time of 5.64 days for the L− group and 2.45 days for the L+ group ($P = 0.04$). Concerning pain relief by laser irradiation, one proposed mechanism is the modulation of nociception by the modification of nerve conduction via the release of endorphins and enkephalins (Franquin, 1993).

Regarding morphine administration, Cowen *et al* (1997) also reported a significant reduction from 5.3 days in the control group to 3.2 days in the group with laser irradiation. Although we did not observe a significant difference in the duration of morphine administration, our study noted quite a remarkable difference in morphine incidence: 10 (40.0%) patients in the L− group *vs* 4 (16.67%) patients in the L+ group ($P = 0.07$).

In this study, we used retrospective controls (laser− group) that did not realize laser therapy for oral mucositis. All other therapies and chemotherapy regimens according to the tumor were similar in both groups. Despite the small and heterogeneous characteristic of our sample, the LEL therapy, a noninvasive technique, seems to promote pain relief, reduce the severity of oral mucositis, and decrease morphine administration. However, for a better understanding of the LEL therapy, prospective randomized controlled studies are needed to confirm the effect of this therapy on oral mucositis.

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