Original Article

Low Energy Laser in Prevention of Oral Mucositis in Patients Receiving Radiotherapy and/or Chemotherapy in Pernambuco Cancer Hospital

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Abstract

Oral mucositis induced by antineoplastic therapy causes wide-range pain and discomfort resulting in decreased quality of life. The present study evaluated the benefits of low intensity laser and 0.12% chlorhexidine gluconate in the prevention of oral mucositis induced by radiation, associated or not with chemotherapy, and considered degrees/severity, time of appearance of the lesions and functional loss. Eighty-four outpatients were considered and 49 were included in this study and divided into two groups: Group 1 received laser treatments in three stages, starting three days before treatment until the end of therapy. Group 2 was instructed to do daily mouth rinses with chlorhexidine gluconate. The prevalence of clinical mucositis was 49%, and of functional mucositis, 28.6%, when the two groups were considered together. This percentage was smaller in the laser group, 44% for the clinical mucositis group and 24% for the functional. The two protocols were well tolerated and showed benefits, mainly from the point of view of functionality, and delayed the onset and development of mucositis.

Keywords: Preventive dentistry. Chlorhexidine. Mucositis. Radiotherapy. Chemotherapy. Neoplasms. Laser.

Introduction

Cancer still continues to be a great scourge for mankind and a huge challenge for scientists. Not infrequently, it is diagnosed in its late stages and its treatment can result in side effects and sometimes poor outcomes. Surgery, radiotherapy and chemotherapy, associated or not, can be used to treat head and neck cancer. However, neither radiotherapy nor chemotherapy are able to distinguish normal from tumor cells that multiply at a great speed, leading in some circumstances to alterations of the oral mucosa. Oral mucositis represents one of the major complications of antineoplastic management, resulting in suffering and pain, reduced quality of life, and sometimes interfering with the continuity of the treatment. Low intensity Laser has been used for prevention and treatment of radio and chemotherapy-induced oral mucositis, and it is recognized as a non-traumatic technique that stimulates cellular proliferation and helps in the analgesic and scarring processes. Chlorhexidine is a potent antiseptic and broad-spectrum antimicrobial that has been studied for the improvement in quality of oral health of patients with head and neck neoplasms, for the prevention of oral mucositis and superinfection. There is no universally accepted guideline for the prevention of anticancer

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therapy-induced oral mucositis. The present study aims to evaluate the benefits of the use of Laser therapy and gluconate chlorexide 0.12% in the prevention of oral mucositis secondary to radiotherapy, associated or not to chemotherapy, taking into account grade/severity, time of lesion appearance and functional loss.

Literature Review

There is no available systemic antineoplastic treatment up to now that is able to destroy cancer cells without damaging normal ones. Rapid tissue renewal, e.g. oral epithelium, is especially susceptible to it. Therefore, the mouth is a common and visible site of the complications related to cancer therapy.[1-2] Oral mucositis is a clinical condition characterized by erithema, ulceration and pain, which are common complications of therapeutic procedures involving chemotherapy or chemoradiotherapy,[3-8] ranging from 80%-100%.[9-10] Initial symptoms are a burning sensation[11-12] and increased sensibility to hot and spicy foods11 recognized as the major non-hematologic cytotoxic complications of chemo- and radiotherapy. These complications may cause significant morbidity, pain, odinophagy, disgeusy, leading to dehydration and malnutrition, compromising quality of life.

As a consequence of immunosuppression, oral mucositis can result in severe bacterial, viral and fungal infections, as well as systemic infections.[7,13] These complicating factors can modify or even interrupt chemo and/or radiotherapy,[3,13-15] with subsequent loss of the control of tumor growth.[5,16-18] Non-keratinized areas of the mucosa are the most vulnerable sites for direct stomatotoxic action.[11,19-21]

Mucositis may become evident in the second or third week of therapy, and can persist for three to six weeks after the end of therapy.[22] Despite several published studies there is no general consensus up to now as to the prevention of mucositis. Many approaches have been tried, but none have been determined as the best.

Low intensity Laser emits radiation without potential destructive effects with anti-inflammatory, analgesic and biostimulation actions.[23] It acts in cell stimulation, leading to the release, by macrophages, of growth factors, the proliferation of keratinocytes, the increased population of mastocytes, degranulation and angiogenesis. These effects can lead to the acceleration of the wound scarring process, due in part to the reduction in duration of acute inflammation thereby resulting in faster tissue repair.[24] In a study carried out by Barash25 and Cowen et al.,[13] the He-Ne Laser was beneficial in the reduction of the severity of mucositis. According to Bensadoun et al.[14] and Sandoval et al.,[26] the use of the low intensity He-Ne Laser seems to be a simple and non-traumatic technique for the prevention and treatment of mucositis from different etiologies, having the ability to delay its onset and to decrease its duration and peak of severity.

Among the facts involved in the genesis of mucosal alterations induced by radiation, modification of the oral bacterial flora can be found with subsequent development of infection. Therefore, an antiseptic drug could help in the prevention of these changes and decrease the intensity of mucositis.[27] Chlorhexidine is an antiseptic and antimicrobial widely used in odontology, having broad-spectrum bactericidal effects against aerobic and anaerobic bacteria as well as fungus in saliva and dental plaque.[28-29] A study performed by Cheng, Chang and Yuen,[15] showed that chlorhexidine, along with adequate oral hygiene, can reduce mucositis in children treated with chemotherapy. The findings suggested a significant reduction in the incidence and severity of this complication in patients that used chlorhexidine, compared with those who used benzidamine.

Methods

An experimental clinical randomized study was conducted with all the patients seen, from December 2004 to September 2005, at the Head and Neck Surgery Out-patient Clinic of the Cancer Hospital of Pernambuco; all were treated with radiotherapy and some were also treated with chemotherapy. All patients were treated by external radiotherapy at a rate of 1 fraction of 180-200cGy/day 5 days a week. Chemotherapy drugs information was not available on patient's files records.

From the eighty-four patients evaluated, forty-nine completed the suggested protocol for the prevention of oral mucositis. A total of thirty-five patients were excluded from research samples: thirty-one patients did not complete laser application protocol, one patient was transferred to another hospital, two has given up radiotherapy, and one did not want to collaborate with the study. The remaining forty-nine patients were randomly divided in two groups to receive either prophylactic Laser treatment to the oral mucosa or Chlorhexidine Gluconate 0.12% mouth rinse after giving informed consent.

Authorization was requested from the Ethics

Committee of Research on Human Beings at the Cancer Hospital of Pernambuco and Health Science Center of the Federal University of Pernambuco.

The equipment used was PHOTON LASE, model III of DMC, InGaAlP, wavelength of 685 nm, caliber at power 35mW and energy density of 1,1J/cm2.

In group 1, Laser application was performed in a continuous way in three distinct steps: 1) 3 consecutive days before antineoplastic therapy (days -2, -1 and 0); 2) 3 more consecutives applications, 7 days after the onset of combined therapy (day 7) and, for the patients that were treated only with radiotherapy, 10 days after its onset (day 10); 3) continued Laser application, every other day, until the antineoplastic treatment.

Laser application was punctual and distanced one centimeter from each other. Sites were selected excluding tumor area to avoid cellular proliferation in neoplastic area.[30-31] Each of the sites received 32-second consecutive illuminations; the energy density delivered was 1,1J/cm2.

Group 2 patients were instructed to rinse the mouth with 10 ml of Chlorhexidine Gluconate 0.12% solution for 1 minute, twice a day, morning and evening. Mouth rinses were started before the first radiation. All patients received instruction as to adequate oral hygiene and it was suggested to perform mouth rinses with nistatine solution.

All patients were properly identified and data related to gender, age, occupation, address, type and local of tumor, type of treatment, medical history and oral health were recorded. The patients were observed once a week by the researcher and two oral pathologists. At the end of clinical evaluation, mucositis grade was classified and written down in individual files. Mucositis severity was scored by a scale based on clinical features and by the Oral Toxity Scale from the National Cancer Institute. This scale is based on patients ability to swallow (Sandoval et al. 2003).[26] (Table 1)

Caries, periodontal disease, bacterial plaques, radicular remains, metallic restorations or metallic crowns were considered parameters to analyze the patients' oral health. Those with one of those conditions were classified as regular oral health, and patients with two or more of those conditions were classified as poor oral heath.

The severity of mucositis was evaluated clinically, functionally, as regards swallowing ability and pain, in accordance with the scale of the National Institute of Cancer.[26] Only two types of mucositis were considered from the statistic point of view: mild (grade I and II) and severe (grade III and IV), and considered both clinical and functional aspects.

Table 1 - Mucositis evaluation scale

Grade	Type of score	
	Clinical parameters	Functional impairments
0	No change	No symptoms
I	Whitish aspect	Soreness
II	Erythema	Mild pain/ can eat solids
III	White coating	Can´t eat solids/ liquids
IV	Ulcers	Require nutritional eat support

All statistical tests used in this study considered the level of significance of 0.05 (equal or inferior to 0.05), and the software used was STATA version 8.0.

Results

From the forty-nine analyzed patients, forty-five were male (91.8%) and four female. Their mean age was 59.5 years (range 27-86). No statistical difference was observed between the laser group mean age (57.2 years) and chlorexidine group mean age (61.9 years) (Student T-test, p=0.226). No statistical difference was observed between the radiotherapy dosage of the laser group (mean of 6536cGy) and the chlorexidine group (mean of 6605 cGy) (Student T-test, p=0.705).

Twenty-four patients (49%) developed clinical mucositis and 14 (28.6%) developed functional mucositis (p=0.776) (Table 2). Two independent researches evaluated the mucositis of oral mucosa in the sample studied. Kappa index was considered excellent (kappa=0.898 and kappa=0.818).

Table 2 - Distribution of clinical and functional mucositis grades found among the 49 patients.

Type of Mucositis	Grade	N	%
Clinical	Absent	25	51.0
	Mild	13	26.6
	Severe	11	22.4
Functional	Absent	35	71.4
	Mild	7	14.3
	Severe	7	14.3

Tables 3 and 4 show the results of univariated analysis including the grade of clinical and functional mucositis respectively, associated with type of protocol used, general and oral health. The results of the Fisher's Exact Test, indicate that none of these variables showed an statistically significant association with clinical mucositis.

In the Laser group, functional mucositis was absent in 76% (CI 95%: 54.8 – 90.6%). In the Chlorhexidine group, functional mucositis was absent in 66.6% (CI 95%: 44.7 – 84.4%). Although, when compared, both group's results showed no statistical significance (p=1,000).

Table 3 - Results of univaried analysis including the grade of clinical mucositis and the varibles: protocol type, general and bucal health

	Clinical Mucositis								
Variables	**Absent**		**Mild**		**Severe**		**Total**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Protocol									
Chlorhexidine	11	45.8	7	29.2	6	25.0	24	100.0	0.776
Laser	14	56.0	6	24.0	5	20.0	25	100.0	
General health									
Bad	2	50.0	0	-	2	50.0	4	100.0	0.676
Regular	12	54.5	6	27.3	4	18.2	22	100.0	
Good	11	47.8	7	30.4	5	21.7	23	100.0	
Bucal health									
Bad	10	41.7	8	33.3	6	25.0	24	100.0	0.174
Regular	14	70.0	3	15.0	3	15.0	20	100.0	
Good	1	20.0	2	40.0	2	40.0	5	100.0	

Table 4 - Results of univaried analysis including the grade of functional mucositis and the varibles: protocol type, general and bucal health

	Functional Mucositis								
Variables	**Absent**		**Mild**		**Severe**		**Total**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Protocol									
Chlorhexidine	16	66.6	4	16.7	4	16.7	24	100.0	1.000
Laser	19	76.0	3	12.0	3	12.0	25	100.0	
General health									
Bad	3	75.0	0	-	1	25.0	4	100.0	0.304
Regular	16	72.7	5	22.7	1	4.5	22	100.0	
Good	16	69.6	2	8.7	5	21.7	23	100.0	
Bucal health									
Bad	14	58.3	5	20.8	5	20.8	24	100.0	0.038
Regular	18	90.0	2	10.0	0	-	20	100.0	
Good	3	60.0	0	-	2	40.0	5	100.0	

Discussion

The main interest in conducting this research lies in the fact that oral mucositis is a frequent and serious complication in the management of oncologic patients and there is no accepted protocol for its prevention. Laser and Chlorhexidine were chosen because they are both safe and non-invasive techniques, with negligible side effects.

Patients that are submitted to oropharyngeal radiation invariably develop mucositis.[14,17] In our study, the prevalence of clinical mucositis was 49% and functional mucositis was 28.6%, when both groups were considered together. The prevalence was slightly smaller in the Laser group; 44% for clinical mucositis and 25% for functional, showing that patients in this study developed less mucositis when compared to the current literature.

The results showed better oral conditions by the end of the study, considering both clinical and functional aspects, compared to literature. Severe clinical mucositis developed in only 20% of patients in the Laser group and in 25% of Chlorhexidine, consistent with data from Bensadoun et al.,[14] who reported a 33% reduction in severe mucositis (III and IV) in patients treated with Laser. From the functional point of view, the percentage was smaller, represented by 12% in the Laser group and 16.7% in the Chlorhexidine group. Despite the absence of a control group, when these results were compared with the literature in which severe mucositis was seen in about 75-80% after head and neck radiation[5,21] or in more than 90%, according to Merlano et al.,[32] it can be considered satisfactory.

In the Laser group, 76% of the patients did not develop functional mucositis, Confidence Interval (CI 95%) of 54.8 to 90.6%, resulting clearly in a better quality of life for the patients of this group, when compared to the Chlorhexidine group (66.6%; CI 95%:44.7-84.4%). In the Cowen et al. study,[13] patients treated with Laser reported better ability to swallow.

Chemotherapy manifestations develop after a few days of treatment.[2,6,12,33] Radiation mucositis can be seen during the second or third week of treatment.[2,5,14,34] In our study, the average time for the emergence of mucositis in patients who received combined therapy was 3.5 weeks, and in those who received only radiotherapy it was 4.8 weeks, in the Laser group 4.44 and 5.08 in the Chlorhexidine group.

Laser applications were well tolerated and there were no side effects, a result consistent with Bensadoun et al.[14] and Eduardo.[35] Despite the unpleasant taste of Chlorhexidine, there were no complaints from the patients.

The results showed that although neither Laser nor Chlorhexidine are able to eliminate alone pain in all patients its frequency was smaller in both groups when compared to the literature. It is possible to say that there is a tendency of the utilized protocols to lessen painful symptoms during radiotherapy. Since their mechanisms of action are different, it is also possible to say that if used concomitantly, a greater reduction in pain and, consequently, improved quality of life, can be expected.

Conclusions

Despite our small sample, it is evident that Low Intensity Laser and Chlorhexidine Gluconate 0.12% are noninvasive techniques that seem to promote pain relief, reduce severity and delay the development of oral mucositis. The results showed benefits for the studied groups, especially from the functional point of view. These benefits could be more expressive if they were used concomitantly (Laser + Chlorhexidine), since they have different mechanisms of action.

Further randomized controlled multicentric studies with homogenous samples and different Laser application schedules should be conducted with the aim to develop effective protocols in the prevention and treatment of a debilitating complication such as oral mucositis.

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