Original Article

Low Level Laser Therapy in Management of Chemotherapy-Induced Oral Mucositis: Prophylaxis or Treatment?

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Abstract:

Introduction: Chemotherapy-induced oral mucositis (COM) is a common, debilitating complication of cancer therapy. The aims of this study were to evaluate the effect of low level laser therapy (LLLT) on prevention of COM in patients with hematologic malignancies.
Methods: Fifty-five patients hospitalized to undergo chemotherapy in Imam Hospital were included into the study. These patients were divided into two groups. The oral cavity of the patients were illuminated by continues laser beam using a GaAlAs laser device with wavelength of 630 nm, power output 30 mW, and dose of 5 J/cm^2 for six days (LLLT group). The patients in the second group underwent placebo irradiation (power output equal to zero) with the similar protocol. The severity of the COM was clinically evaluated based on WHO grading scale. The patientys' quality of life was assessed before and after the intervention according to EORTC QLQ-C30 questionnaire.
Results: The incidence of COM in LLLT group (31%) was less than the placebo group (41%). Mean duration of COM healing was 4.8 and 12 days in LLLT and placebo groups, respectively (p=0.03). Xereostomia was significantly less severe in LLLT group in comparison with the placebo group (p=0.007).
Conclusion: Our findings showed that LLLT significantly reduced the incidence of oral mucositis of WHO grade 3 and 4 as the most debilitating form of oral mucositis, in which oral alimentation is impossible. Also, LLLT could reduce duration of oral mucositis, decreased the risk of secondary infection, and accelerated return to normal nutrition.
Keywords: Lasers; Laser Therapy, Low Level; Mucositis, Oral; Chemotherapy; Quality of life; Disease Management; therapy; Prophylaxis

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Introduction

Although modern modalities are increasingly being used in cancer treatment, chemotherapy has yet remained the mainstay of treatment for patients with advanced malignant disease incurable by local surgery or radiotherapy (1). Effective use of chemotherapy is limited by its toxic effects including nausea and vomiting, diarrhea, mucositis, and myelosuppression (1). Oral mucositis is a

common, debilitating complication of cancer chemotherapy and radiotherapy, occurring for about 40% of the patients (2). It is associated with a higher risk of infection, pain, chemotherapy-dose reduction, and infection-related death (3-4). Furthermore, severe mucositis commonly results in compromised nutritional intake and quality of life (4). Therefore, there has been increasing emphasis on prevention and treatment of mucositis.

Nowadays, management of oral mucositis is generally based on palliation of the symptoms and prevention of secondary infections. No standard therapy has been found to be able to prevent or treat severe oral mucositis, yet (5). Recently, there have been many attempts to find new modalities to prevent oral mucositis due to cancer therapy (6). Regarding the physiopathology of oral mucositis, it is necessary to consider managements with mechanisms of action that match with those biological mechanisms involved in each phase of mucositis. Unfortunately, so far, the prevention and therapy of oral mucositis have been mainly empiric, encompassing a wide variety of means such as basic oral care, bland oral rinses, analgesics, antibiotics, cryotherapy, local anesthetics, growth factors and cytokines, biologic mucosal protectants, anti-inflammatory agents, and complementary and alternative medicines. Thus, searching for a new alternative prophylactic modality seems quite rational.

Nonpharmacologic therapies, such as low level laser therapy (LLLT), may also be effective as an adjuvant therapy for the management of oral mucositis (6-11). However, because of the significant placebo response rate in any clinical trial, these therapies require careful investigation to ascertain their effectiveness. By definition, LLLT takes place at low irradiation intensities. Therefore, it is assumed that any biological effects are secondary to direct effects of the photonic radiation and are not the results of thermal effects (12). Many experimental and clinical studies have reported the benefits of LLLT on tissue healing (13-15); however, others have shown no effect (16). These conflicting results are likely due to variations in many factors including laser irradiation parameters (e.g. wavelength, power density, and fluence) and design/setting of the studies (e.g. comparison of heterogeneous clinical situation, lack of control groups, and limited or no blinding of the investigators) (17).

The mechanism by which LLLT accelerates wound healing may be due to increased mitochondrial ATP production, the local release of growth factors (18-19), increased proliferation of fibroblasts, (20-21) or production of collagen (20). Low level laser irradiation was found to induce a significant increase in skin microcirculation, as measured by infrared thermography (22). It has been suggested that LLLT may be capable of detoxifying oxygen free radicals or reducing the formation of these free radicals during chemotherapy and radiotherapy. The consistent reports of active oxygen radical productions by chemotherapeutic agents and consequent inflammatory responses generated by these agents might explain, at least in part, the potential prophylactic role for LLLT in oral mucositis due to its anti-inflammatory effects (23).

Due to high incidence of oral mucositis, particularly severe and the most debilitating ones in bone marrow transplant patients, most of the studies have been focusing on these patients. Almost all of these studies showed that LLLT was used as a well-tolerated and safe modality to reduce the severity and pain scores of oral mucositis. However, it is necessary to find out whether LLLT has similar effects on patients undergoing milder chemotherapy regimes for other reasons. Therefore, we are going to test the hypothesis whether LLLT (λ=660 nm) might be capable of decreasing the incidence of oral mucositis and improving the quality of life in these patients.

Methods

Study Design

This study was designed as a double-blind randomized placebo clinical trial (Figure 1). The protocol was reviewed and approved by Medical Ethics Board in Medical Sciences/University of Tehran, Iran. The sampling was carried out on patients receiving chemotherapy for hematological malignancies at Hematology and Oncology ward, Imam Khomeini Hospital, Tehran, Iran from June 2005 to November 2006. The participants were enrolled into this study after coinciding with inclusion and exclusion criteria and obtaining written informed consents.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) patients aged between 20-60 years with hematological malignancy receiving chemotherapy, 2) Karnofsky performance status scale ≥ 60, 3) life expectancy more than 3 months, 4) white blood cells≥1500 cell/mm^3, 5) platelet count≥100,000 cell/mm^3, 5) the ability to give informed consent, understand instructions, and co-operate in treatment. Patients with pervious or concurrent head and neck radiotherapy, pervious head and neck surgery, denture or oral prosthesis, pregnancy, or photosensitivity were excluded.

Procedure

On admission, enrolled patients were instructed to stop smoking tobacco and drinking alcohol and improve their daily oral hygiene. Oral examination and preventive dental management were performed prior to chemotherapy. After history taking and physical examination, the participants were randomly divided into two groups using a block randomization with a manual schedule; group A: active laser and group B: sham laser. Patients were blinded towards the therapeutic protocol of their groups.

Laser irradiation was performed with the Gallium-Aluminum-Arsenide (GaAlAs, Lasertronics, wavelength 660 nm, 30 mW, continuous wave) laser. The power output was calibrated with a thermopile power meter (Gentec Electro Optics Inc., Canada). Patients were irradiated daily for 5 days (Saturday to Wednesday) per week for 4 successive weeks starting from the beginning day of chemotherapy course. At each treatment session, a series of standardized fields including ten points in the posterior third of the internal surfaces of the cheeks, soft palate, and anterior tonsillar pillars were irradiated (Bensadone et al 1989). Each laser treatment area occupied 1 cm^2 of the surface. In the active laser group, patients were irradiated with the probe emitting dose of 10 J/cm^2 while participants in the sham laser group were irradiated with the same, but inactive probes. Approximately, a period of ten minutes was needed to cover the entire area of therapy for each patient. The therapist and the patients both wore protective goggles during the treatment for safety and ensuring the double blindness.

Table 1. World Health Organization staging for oral mucositis

Definition	Stage
None	0
Soreness ± erythema	1
Erythema, ulcers; patient can swallow solid food	2
Ulcers with extensive erythema; patient cannot swallow solid food	3
Mucositis to the extent that alimentation is not possible	4

Outcome Measures

Oral mucositis was graded using World Health Organization staging for mucositis by a blinded physician (Table 1). The primary endpoints were the incidence and duration of oral mucositis, especially severe ones (grade 3 and 4). The duration was considered to be zero days among patients who did not have oral mucositis.

The secondary endpoint was quality of life according to the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 is a 30-item core-cancer-specific questionnaire measuring quality of life in cancer patients, and conceptual and methodological issues underlying the construction of the questionnaire are described in detail elsewhere by the researchers who pioneered it. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality of life scale. We used Farsi translation of the questionnaire validated in previous studies (Montazeri 1999).

Statistical Analysis

Analysis was based on intention to treat. Data was analyzed using SPSS version 13. In order to determine the normal distribution of the quantitative variable, we drew the histogram curve of the variable and used Kolmogorov Smirnov test. We used student t test and chi square test. The level of statistical significance was set at a two-tailed p-value of 0.05.

Results

Twenty seven patients in LLLT group and 28 patients in sham group completed the study. Baseline characteristics of the patients in both groups were shown in table 2. The distribution of sex and age

Table 2. Demographic and baseline characteristics of the Patients

	LLLT (n=27)	Placebo (n=28)	p-value
Gender, N (%)			
Male	16	11	0.234
Female	11	17	
Age, mean ± SD, years	27.3±9.7	29.7±11	0.402
Diagnosis, N (%)			
AML	13	15	0.097
ALL	6	9	
Hodgkin	2	-	
Lymphoma	2	1	
Multiple Myolema	1	1	
Germ Cell Tumor	-	1	
Pervious Chemotherapy, N (%)	10 (24%)	6 (12%)	0.203
Pervious oral mucositis, N (%)	7	4	0.281
Karnofsky performance status, N (%)			
60	2 (7%)	1 (3%)	0.972
70	2 (7%)	2 (7%)	
80	5 (18%)	7 (25%)	
90	15 (57%)	16 (60%)	
100	3 (11%)	2 (7%)	

was not significantly different between the two groups. The most common diagnosis of the patients was acute leukemia (AML and ALL). Ten patients in LLLT group had a history of chemotherapy, seven of whom, had experienced oral mucositis. In the sham group, only six patients had pervious chemotherapy and four of them reported oral mucositis. All patients had Karnofsky performance status more than 60%, as it was one of inclusion criteria of the study.

According to the WHO grading scale, the incidence of oral mucositis was not significantly lower in LLLT group in comparison to the sham group (55% vs. 62%, p=0.36), but the incidence of grade 3 and 4 oral mucositis was 10% in the sham group, while, in the LLLT groups, no oral mucositis of grade 3 and 4 was reported (p>0.05). The mean duration of oral mucositis was significantly shorter in 15 patients in the LLLT group versus 17 patients in the sham group (4.8±1.6 vs. 12±6.7 days, p=0.031). The scores of QOL-C30 were demonstrated in table 3. There were no significant differences between the two comparative groups regarding functional scales and symptom scales.

Discussion

This study provides evidence that LLLT can significantly reduce, in a clinically significant way, the duration and incidence of oral mucositis after chemotherapy in patients with hematologic malignancies. This technique consistently decreased the incidence of severe oral mucositis.

Recently, several studies have tried to obtain adequate evidences for effectiveness of LLLT on prevention and treatment of oral mucositis due to cancer therapies including chemotherapy and radiotherapy and autologous hematopoietic stem-cell transplantation. The Multinational Association for Supportive Care in Cancer (MASCC) and the

Table 3. Quality of life assessment before and after chemotherapy (QLQ-C30)

	Laser group (n=16)		Placebo group(n=17)	
	Before	After	Before	After
Functioning scales				
Physical	52 ± 28.3	53.8 ± 27.5	68.2 ± 14.4	63 ± 18.1
Role	51.2 ± 30	46.1 ± 29.7	64.1 ± 24.3	57.6 ± 30.1
Cognitive	76.9 ± 12.7	73 ± 17.3	73 ± 22	71.7 ± 13.4
Emotional	51.2 ± 23	53.8 ± 19.1	50.6 ± 19	49.3 ± 19.6
Social	34.6 ± 27.6	43.5 ± 27.6	34.6 ± 27.6	33.3 ± 27.2
Global quality of life	51.2 ± 7.4	48.7 ± 15.9	62.1 ± 20	61.5 ± 24.6
Symptom scales				
Fatigue	58.1 ± 17	57.2 ± 16.2	34.1 ± 19.4	41 ± 14.6
Nausea & vomiting	16.6 ± 13.6	21.7 ± 17.1	7.6 ± 12.9	26.9 ± 12.7
Pain	53.8 ± 31.2	47.4 ± 28.7	15.3 ± 24	16.6 ± 28
Dyspnea	30.7 ± 21.3	38.4 ± 29.9	20.5 ± 25.5	30.7 ± 21.3
Sleep disturbance	41 ± 24.1	46.1 ± 32	48.7 ± 32.2	46.1 ± 28.9
Appetite loss	46.1 ± 12.5	46.1 ± 32	51.2 ± 29.2	43.5 ± 21
Constipation	15.3 ± 37.5	10.2 ± 23	5.1 ± 12.5	0
Diarrhea	2.5 ± 9.2	12.8 ± 21	10.2 ± 16	12.8 ± 16.8
Financial impact	69.2 ± 34.5	61.5 ± 29.9	66.6 ± 30.4	71.7 ± 26.6

International Society of Oral Oncology (ISOO) organized a "Mucositis Consensus Conference" during 2006, updating initial guidelines published by the same group in 2004 with complete literature review, to draw guidelines for evidence-based management of oral mucositis during chemotherapy and radiotherapy.

In this report, LLLT is addressed as a very promising investigational method, regarding its current encouraging results. Due to high incidence of oral mucositis (particularly severe ones in bone marrow transplant patients), the most debilitating form of oral mucositis in theses patients, in which oral alimentation is impossible, has been focused in most studies. Approximately, all of these studies emphasized that LLLT was used as a well-tolerated and safe modality to reduce the severity of oral mucositis and pain scores. However, it is necessary to known whether LLLT has similar effects on patients undergoing chemotherapy. The incidence of oral mucositis due to chemotherapy alone was estimated to be about 40%. In our study, the incidence in placebo participants was approximately 60%, which could be explained by the type of the protocol and regimes of chemotherapy and patients' susceptibility.

Conclusion

Low level laser therapy significantly reduced the incidence of grade 3 and 4 oral mucositis as the most debilitating form of oral mucositis with impossible oral alimentation. Also, LLLT could reduce duration of oral mucositis, decreased the risk of secondary infection, and accelerated return to normal nutrition.

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