Evaluation of the Effect of Low Level Laser on Prevention of Chemotherapy-Induced Mucositis

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Abstract- Radiotherapy in the head and neck region and chemotherapy might give rise to oral mucositis which is a severe and painful inflammation. There is no known definite cure for mucositis. A number of studies have attempted to evaluate the effect of low-power laser on radiotherapy- and chemotherapy-induced mucositis. The present study was undertaken to evaluate the effect of low-power laser on the prevention of mucositis, xerostomia and pain as a result of chemotherapy. The subjects in this double-blind randomized controlled study were 24 adult patients who underwent chemotherapy during 2009-2010. The results showed that low-power laser was able to decrease the effect of chemotherapy on oral mucositis, xerostomia and pain in a variety of malignancies (P<0.05). It can be concluded that low-power laser might decrease the intensity of mucositis.

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Keywords: Chemotherapy; Low level laser; Mucositis

Introduction

Oral mucositis is one of the serious complications of patients receiving radiotherapy or chemotherapy. There are reports that around 40% of patients with different cancers, who undergo chemotherapy and bone marrow transplantation, develop oral mucositis (1).

Oral mucositis is believed to be the result of a complicated biologic process involving direct damage to the oral epithelium during cell division, decrease in basal cell counts in the epithelium, the immune system modulation weakness, intensification of the inflammatory processes, and super infection by the oral bacterial flora (2).

Oral mucositis gives rise to a painful inflammatory process, which might be debilitating and might necessitate the use of opioid analgesics for pain relief (3). As a result of severe pain the patients might turn to intestinal or venous nutrition because they do not enjoy oral nutrition. Severe mucositis might have a detrimental effect on the patients’ therapeutic protocol, necessitating the cessation of the treatment in some cases (4). Moreover, mucositis may induce vomiting, diarrhea, sleep disturbances, anorexia (5), weight loss and a decrease in the quality of life (6).

Chemotherapy-induced mucositis in the non-keratinized mucosa is usually manifested in the first and second weeks of chemotherapy sessions, subsiding during the third or fourth weeks after chemotherapy. Mucositis-induced pain leads to disorders in deglutition and normal oral cavity functions. These disorders, in conjunction with xerostomia, increase the odds of opportunistic infections (7). Mucositis is often managed by the administration of chlorhexidine (8), sodium carbonate (9), and saline mouthwashes (10), and local anesthetics such as diphenhydramine (11), promethazine mixed with manganese milk, covering agents such as sucralfate (12), and anti-inflammatory agents such as Matricaria recutita (chamomile) (13), or local steroids (14) and sufficient water. However, there is no definite cure for mucositis (4).

Low-power lasers have various uses in medicine, including acceleration of wound healing process, treatment of muscular disorders and pain control (15). Low-power lasers induce DNA synthesis in myofibroblasts and conversion of fibroblasts to myofibroblasts, energy production at mitochondrial
level and finally an increase in vascularity and re-epithelialization of injured tissues (15). The anti-inflammatory and analgesic effects of low-power lasers might be attributed to a decrease in pro-inflammatory cytokines, a decrease in free oxygen radicals and alterations in nerve impulse conduction (16,17).

In recent years some researchers have focused attention on the use of low-power lasers to treat and prevent chemotherapy- and radiotherapy-induced oral mucositis. Initial results have demonstrated the beneficial effects of laser therapy on prevention and treatment of radiotherapy-induced oral mucositis. However, there are only a limited number of studies on chemotherapy-induced mucositis and its prevention.

Materials and Methods

This randomized double-blind controlled study was carried out on 48 adult patients. The subjects were 18 years old and older, who were under chemotherapy for the first time in their lives during 2008-2009.

Inclusion criteria

The inclusion criteria were: chemotherapy treatment regimen with the same mucositis probability; Karnofsky performance status case $\geq 60$; life expectancy $\geq 6$ months; white blood cell count $\geq 1500$ cell/ml and platelet count $\geq 100000/\mu l$.

Exclusion criteria

The exclusion criteria included: previous or ongoing radiotherapy in the head and neck region, including nasopharynx, oropharynx, and larynx; previous head and neck surgery due to malignancy; denture use; pregnancy; and infection.

The subjects were selected from patients referred to the Department of Oncology at Zahedan Imam Ali Hospital (Iran).

The subjects were divided into two laser-on and laser-off groups with the use of 4-block sets using block randomization method.

In the laser group the subjects underwent laser therapy prior to each episode of chemotherapy, which consisted of irradiation with 630 nm low-power laser with 30 mW output power. The energy dose for laser therapy is 5 J/cm². The irradiated areas included 10 spots in the oral cavity: two spots on the cheeks, two on the tongue, two on the floor of the mouth, one on the soft palate and one on the hard palate.

In the laser-off group, laser therapy was carried out with the equipment “off” during the same time. Protective eye shields were used to avoid detrimental effects of the beam on eyes and to keep the subjects blind to the procedures involved.

Each group consisted of 24 patients who were followed until the end of the chemotherapy phase. All the patients were instructed in oral hygiene, including drinking a lot of water, toothbrushing with a soft toothbrush after meals, and abstinence from alcohol, smoking cigarettes, hot or cold drinks, and eating very spicy, acidic and tough foods during chemotherapy(1).

The subjects’ mucous and salivary health was checked by an oral medicine specialist before the chemotherapy phase. Two weeks after chemotherapy was initiated and every two weeks until the end of chemotherapy sessions, a student of dentistry and an oral medicine specialist monitored mucositis, xerostomia and pain. They were blind to randomization and laser therapy. The patients were examined under illumination, using dental explorers and mirrors. Data was recorded in forms specially designed for the purpose of the study. Oral mucositis patients were graded from 0 to 4, using World Health Organization (WHO) criteria (20); xerostomia was graded from 1 to 4 (Table 1) (21).

Pain was evaluated based on visual analog scale. In this system, zero indicates no pain and ten indicates severe pain. Patients showed intensity of their pain on a ruler. The patients were asked to select a number from 1 to 10 to express the intensity of pain they experienced.

Ethics

The Ethics Committee of Zahedan Medical Sciences University reviewed and approved the study protocol before the patients enrolled. All the patients filled out and signed consent forms. This study is registered on Iranian registry for clinical trials and its registry number is IRCT138811033133N1 (available online at http://www.irct.ir/ and www.who.int/trialsearch/trial).

Statistical analysis

Data was analyzed by SPSS 17 software. Mann-Whitney $U$-tests were used for the purpose. $P$-value mentioned as 0.005 for Mann-Whitney test (for prevention of repeated measurement error, we divided $\alpha$ into 10).

Table 1. Objective grades of xerostomia according to the LENT SOMA scale.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal moisture</td>
</tr>
<tr>
<td>2</td>
<td>Scant saliva</td>
</tr>
<tr>
<td>3</td>
<td>Absence of moisture; sticky, viscous saliva</td>
</tr>
<tr>
<td>4</td>
<td>Absence of moisture; coated mucosa</td>
</tr>
</tbody>
</table>
Table 2. Demographic characteristics of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laser on group</th>
<th>Laser off group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n)</td>
<td>Male 12</td>
<td>Male 12</td>
</tr>
<tr>
<td></td>
<td>Female 12</td>
<td>Female 12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Range 17-72</td>
<td>18-79</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 44.5 ± 4.04</td>
<td>46.2 ± 4.4</td>
</tr>
<tr>
<td>Tumor site (n)</td>
<td>Lung 4 (16.6%)</td>
<td>Lung 4 (16.6%)</td>
</tr>
<tr>
<td></td>
<td>Lymphoma 2 (8.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>GI 2 (8.3%)</td>
<td>GI 8 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>Skin 1 (4.1%)</td>
<td>Skin 2 (8.3%)</td>
</tr>
<tr>
<td></td>
<td>Breast 15 (62.5%)</td>
<td>Breast 10 (41.6%)</td>
</tr>
</tbody>
</table>

Results

On the whole, 48 patients in two groups of 24 were evaluated according to inclusion and exclusion criteria. Demographic data of the patients is presented in table 2. As it can be seen in the table, distribution of age, gender and type of disease were the same in both groups. The analytical results of this study for mucositis, xerostomia, and degree of pain are presented as follows:

Mucositis intensity

At baseline none of the patients exhibited any mucositis symptoms. In the first meeting in the second week of chemotherapy phase, there were statistically significant differences in mucositis intensity between the two groups (P<0.005) (Table 3). In the laser on group mucositis intensity was zero in 14 patients (58%), one in 8 patients (33%) and two in 2 patients (8.3%); however, in the laser off group mucositis intensity was one in 2 patients (8.3%), two in 12 patients (50%) and three in 10 patients (41.6%).

Xerostomia intensity

One week before the study was initiated, patient xerostomia was evaluated. Patients’ salivary flow rates were in the normal range, with no statistically significant differences between the two groups under study (P=0.13). In the first meeting during the second week of chemotherapy phase, there were statistically significant differences in xerostomia intensity between the two groups: xerostomia intensity in the laser on group was less than that in the laser off group (P<0.005). In the laser on group xerostomia intensity grade was one in 10 patients (41.6%), two in 12 patients (50%) and three in 2 patients (8.3%); in the laser off groups xerostomia intensity grade was two in 6 patients (25%), three in 12 patients (50%) and four in 6 patients (25%) (Table 4).

Intensity of pain

Patient pain intensity exhibited statistically significant differences between the laser on and laser off groups, indicating that pain in the laser group was less intense than that in the laser off group (P<0.05). Pain intensity grade in the laser group was zero in 12 patients (50%), one in 8 patients (33.3) and two in 4 patients (16.6%). In the control group pain intensity grade was two in 10 patients (41.6%) and three in 14 patients (58.3%) (Table 5).

Table 3. Mucositis grades in both groups of patients.

<table>
<thead>
<tr>
<th>Mucositis</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
<th>Week 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser on</td>
<td>Mean</td>
<td>0.25</td>
<td>0.5</td>
<td>0.5</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>95%CI</td>
<td>0.13-0.6</td>
<td>0.5-1.1</td>
<td>0.5-1.1</td>
<td>0.5-0.8</td>
<td>0.5-0.8</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Laser off</td>
<td>Mean</td>
<td>2.28</td>
<td>2.3</td>
<td>2.20</td>
<td>1.96</td>
<td>1.96</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>95%CI</td>
<td>1.9-2.5</td>
<td>2.0-2.6</td>
<td>2.0-2.6</td>
<td>1.8-2.05</td>
<td>1.8-2.05</td>
<td>1.3-1.8</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4. Xerostomia intensity in both groups of patients.

<table>
<thead>
<tr>
<th>Xerostomia</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
<th>Week 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser on</td>
<td>Mean</td>
<td>1.3</td>
<td>0.7-1.5</td>
<td>1.12-2.2</td>
<td>1.12-2.2</td>
<td>1.4-2.26</td>
<td>1.12-2.2</td>
<td>0.8-2.5</td>
</tr>
<tr>
<td></td>
<td>95%CI</td>
<td>1.16</td>
<td>0.7-1.5</td>
<td>1.12-2.2</td>
<td>1.12-2.2</td>
<td>1.4-2.26</td>
<td>1.12-2.2</td>
<td>0.8-2.5</td>
</tr>
<tr>
<td>Laser off</td>
<td>Mean</td>
<td>1.25</td>
<td>3.5</td>
<td>3.12</td>
<td>3.25</td>
<td>3.00</td>
<td>2.87</td>
<td>2.75</td>
</tr>
<tr>
<td></td>
<td>95%CI</td>
<td>0.8-1.6</td>
<td>3.05-3.2</td>
<td>2.8-3.4</td>
<td>2.94-3.8</td>
<td>2.5-3.9</td>
<td>2.33-3.4</td>
<td>2.15-3.34</td>
</tr>
<tr>
<td>P-value test</td>
<td></td>
<td>1</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>
**Discussion**

The aim of the present study was to find out whether low-power laser is able to decrease the oral mucositis symptoms and signs in patients undergoing chemotherapy due to various malignancies.

In this double-blind randomized controlled clinical trial an attempt was made to answer the question whether or not low-power laser can prevent mucositis in patients undergoing chemotherapy. The results showed that laser therapy with a wavelength of 630 nm significantly prevents mucositis in these patients. In the present study 100% of the subjects in the control group developed mucositis with various degrees and severity; however, 58% of the subjects in the laser therapy group were not affected by mucositis. In addition, severe grade 3 mucositis was observed only in the control group, which might reflect the possibility that 630 nm laser beam with an output power of 5 J/cm² can prevent mucositis.

None of the subjects in the laser group experienced any pain; however, all the subjects in the control group experienced pain with a degree higher than 5, demonstrating the effect of laser therapy on decreasing pain severity. Although the use of low-power laser did not prevent xerostomia, severe grade 3 xerostomia was only observed in the laser off group, which might reflect the possibility that 630 nm laser beam can prevent severe xerostomia.

The results of the present study are consistent with those of the majority of studies in this regard. Ciais *et al.* demonstrated for the first time in 1984 in a non-randomized study that low-power lasers can decrease the severity of oral mucous lesions (18). In another study by Bensadoun *et al.* from September 1994 to March 1998, 30 patients were randomly selected. The patients underwent low-power laser therapy on the first day of radiotherapy, which consisted of irradiation of 9 points in the oral cavity. Objective evaluation of mucositis grades was carried out by an individual blind to the procedures. The subjects in the control group had grade 3 mucosis 5 times more than the subjects undergoing low-power laser therapy. Pain severity in the case group was significantly lower than that in the control group: recovery period was also shorter in the case group (19).

In a preliminary study in the United States by Cowen *et al.* in 1997, 20 volunteers with different kinds of cancer and treatment protocols were assigned to the control group and another 16 were assigned to the laser group. The results showed that the recovery period of mucous lesions in the laser group was 8.1 day compared to 19.3 days in the control group, demonstrating a statistically significant difference (20).

In a study carried out by Wong and Smith in 2002, 15 patients who had developed grade 2 and 3 mucositis during chemotherapy continued the therapy and underwent laser therapy, too. All the patients received oral hygiene instructions and underwent laser therapy 24 hours prior to chemotherapy and on a weekly basis afterwards. Eleven patients had grade zero mucosis, three had grades 1-2, and one had grade 3-4. In this context, it was concluded that laser therapy decreases the incidence and severity of chemotherapy-induced mucositis: it is also effective for its treatment (21).

In a study by Sandoval *et al.* in 2002, 18 patients who had developed mucositis during chemotherapy, radiotherapy or chemoradiotherapy, underwent low-power laser therapy. Oral mucositis severity was measured before and after laser therapy with OMAS (oral mucositis assessment scale) based on clinical features, and with oral toxicity scale based on the ability to swallow, and pain severity based on visual analog scale. Grade 3 functional mucositis (inability to swallow liquids and solid foods) decreased in 42.85% of the cases. In addition, grade 4 clinical mucositis (ulceration) decreased in 75% of the cases. An immediate decrease in pain severity was observed in 12 patients after the first laser therapy session (66.6%). During the final session only two patients experienced no improvement in pain severity (22).
Nes and Posso carried out a study in 2005 to evaluate the effect of low-power laser on pain control in chemotherapy-induced mucositis (23). The subjects consisted of 13 adult patients receiving treatment for cancer. The patients received treatment during a 5-day period and their pain intensity was evaluated before and after laser therapy. After each treatment session each day, on average a decrease of 67% in pain severity was expressed. It was concluded that low-power laser can decrease the severity of mucositis pain induced by chemotherapy (23).

Antunes et al. evaluated the clinical effects of low-power laser on prevention and decreasing the severity of oral mucositis in transplanted hematopoetic stem cells in 2004 and 2005 (24). Evaluation of mucositis was carried out using OMAS and WHO criteria in two groups. According to WHO criteria 94.7% of the patients had mucositis grades of ≤2; however, in the control group, 31.5% of the patients had mucositis grades of ≤1. According to OMAS, 5.3% of the patients in the laser group had ulcerations whereas 73.6% of the patients in the control group had ulcerations.

In a study carried out by Maiya et al. in 2006 patients with stage II-IV oral cavity carcinomas were selected (15). The results of the study demonstrated a significant difference in pain and mucositis between the two groups. Six weeks after radiotherapy, means of pain severity and mucositis grades were significantly lower in both groups. According to WHO criteria 94.7% of the patients had mucositis grades of ≤2; however, in the laser group, 31.5% of the patients had mucositis grades of ≤1. According to OMAS, 5.3% of the patients in the laser group had ulcerations whereas 73.6% of the patients in the control group had ulcerations.

References
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