Effect of Low Level Laser Therapy During the Treatment of Chemotherapy Induced Oral Mucositis in Postmenopausal Breast Cancer

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ABSTRACT

Background: Oral mucositis (OM) is a common complication of chemotherapy that causing therapeutic modifications due to patient's debilitation, which often interferes with the prognosis of the disease. Low level laser therapy (LLLT) has a good effect in accelerating wound healing and reducing inflammation. Purpose of the study: to investigate the chemotherapy induced OM responses to (LLLT). Methodology: 30 postmenopausal breast cancer women underwent mastectomy and treated by chemotherapy participated in this study and randomly assigned into 2 groups, group (A) received LLLT for 14 sessions daily, while group (B) received placebo LLLT. Mucositis severity was scored by oral mucositis scale from the National Cancer Institute based on clinical features and functional impairments before and after laser therapy. Results: OM based on the functional scale, mucositis grade III (not capable to eat solids) was reduced in (60 %) of the cases of the study group and also grade IV (require nutritional support) was reduced in (33.3%) versus (20%) and (33.3%) increase in the control group respectively. According to the scale based on the clinical features, in the study group mucositis grade III showed (20%) reduction and grade IV (ulcerative lesions) was reduced in (83.3%) versus (50%) increase in grade IV and no change in grade III in the control group. Conclusion: LLLT is an effective, non invasive, safe and easy to perform in reducing chemotherapy induced oral mucositis.

Key words: Laser, Oral mucositis, chemotherapy, breast cancer.

INTRODUCTION

Breast Cancer constitutes a major public health issue globally with over 1 million new cases diagnosed annually, resulting in over 400,000 annual deaths and about 4.4 million women living with the disease. It is the commonest site specific malignancy affecting women and the most common cause of cancer mortality in women worldwide.

Breast cancer and its treatment constitute a great physical, psychosocial and economic challenge in resource limited societies. The hallmarks of the disease are patients presenting at advanced stage, lack of adequate mammography screening programs, and a high morbidity and mortality.

Risk is increased by early menarche, late menopause, obesity in postmenopausal women, and high concentrations of endogenous estrogens. It appears that estrogens can increase, decrease, or have no effect on breast cancer risk, depending on the timing of estrogen exposure. Levels of endogenous sex hormones are also strongly associated with breast cancer risk in postmenopausal women.

Oncologic treatment often involves the use of radiotherapy and/or chemotherapy. A common acute complication of these kinds of therapy is OM which is inflammation of the mucosa of the mouth which ranges from redness to severe ulceration. Approximately 60% of patients receiving conventional radiotherapy for head and neck cancer and more than 90% of patients submitted to combined therapy (concomitant chemotherapy and radiotherapy). In addition, up to 40% of chemotherapy patients develop oral mucositis.

Oral mucositis has a great impact in patient's quality of life during treatment and sometimes may lead to treatment interruptions, resulting in sever consequences in terms of tumor response.

Oral mucositis is linked to the decreased cell renewal in the basal layers of the epithelium, due to the effects of chemotherapy and radiotherapy. It results from the systemic effects of cytotoxic chemotherapy agents and from the local effects of radiation to the oral mucosa.

The symptoms of oral mucositis vary from pain and discomfort to an inability to tolerate food or fluid, it may also limit the patient's ability to tolerate either chemotherapy or radiotherapy, so that may delay the treatment and limit the effectiveness of cancer therapy.

Nowadays, management of oral mucositis is mostly based on palliation of the symptoms (topical anesthetics, anti-inflammatory, systemic analgesic drugs) and prevention of secondary infection by antimicrobial agents. The use of LLLT appears to be a simple, non-traumatic technique for prevention and treatment of chemotherapy or radiotherapy induced mucositis. The LLLT used for activation of epithelial healing. While LLLT used for the treatment as well as prevention of mucositis has some evidence supporting its use, but this intervention has not been conclusively validated by research in Egypt. So, the purpose of the study was to find out the effect of LLLT in treating chemotherapy induced oral mucositis.

**SUBJECTS, MATERIALS AND METHODS**

30 post menopausal women who underwent mastectomy after diagnosis of breast cancer and undergoing chemotherapy were included in the study from National Cancer Institute (NCI), Cairo University. Their ages ranged from 50-60 years. The chemotherapy protocol was (Endoxan, 5Fu, and Adriablastina); a written consent form was obtained from each participant before enrollment in this current study.

The patients were randomly selected and classified into 2 groups. Group (A): consisted of 15 patients received LLLT, performed daily (660 nm wavelength, power 30 mW, 2 J/cm²) for 14 sessions. The treatment time for each application point was 1.5 min.; the total amount of time for each session of laser application (average 35 min.) depends on the extension and number of lesions. The oral cavity regions were treated (the upper lip, the lower lip, buccal mucosa, ventral and lateral tongue, the floor of the mouth and the hard and soft palate). Before the application of laser, the tip was wrapped with a PVC film and after this procedure it was disinfected with 70% of alcoholic solution. For protection all patients received eyeglass to totally block the light to be used during laser application. Group (B): control or placebo group: consisted of 15 patients received placebo LLLT.

Evaluative procedures of OM severity was scored by: A- A scale based on clinical features and functional impairments (oral...
toxicity scale from the National Cancer Institute (NCICTC) as in table (1). This scoring was done before starting the treatment and after the completion of 14 sessions of LLLT.

Table (1): Oral mucositis grading scores.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of sore</th>
<th>Clinical parameters</th>
<th>Functional impairments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>No change</td>
<td>No symptoms</td>
</tr>
<tr>
<td>I</td>
<td>I</td>
<td>Whitish aspect</td>
<td>soreness</td>
</tr>
<tr>
<td>II</td>
<td>II</td>
<td>Erythema</td>
<td>Mild pain can eat solids</td>
</tr>
<tr>
<td>III</td>
<td>III</td>
<td>White coating</td>
<td>Can't eat solids or liquids</td>
</tr>
<tr>
<td>IV</td>
<td>IV</td>
<td>ulcers</td>
<td>Require nutritional eat support</td>
</tr>
</tbody>
</table>

RESULTS

A- OM scoring

The grading system based on functional impairment before laser therapy in the study group, 2 patients presented mucositis grade I (13.3%) while in the control group, 3 patients (20%), 5 patients presented grade II (33.3%), 4 patients in the control group (26.7%), the grade III showed 5 patients (33.3%) in the study group and the control group, 3 patients (20%) presented grade IV as shown in table (2).

Table (2): Shows the number of patients presented in functional and clinical grades of OM pre and post application of LLLT applications in both groups (A and B).

<table>
<thead>
<tr>
<th>Mucositis grades</th>
<th>Functional grades</th>
<th>Clinical grades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group (A)</td>
<td>Group (B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Grade 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade I</td>
<td>2 (13.3%)</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>5 (33.3%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>5 (33.3%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>3 (20%)</td>
<td>2 (13.3%)</td>
</tr>
</tbody>
</table>

After 14 sessions of laser application for the study group, the functional impairment was improved especially in grade III (defined as painful erythema, edema or ulcers and inability to eat solids and liquids) which showed (60%) improvement and also grade IV (require nutritional eat support) showed (33.3%) improvement as shown in fig. (1).
In the control group, (120%) increase in the patients presented grade III and (133.3%) increase in grade IV.

The mucositis grades based on clinical aspects, in the study group, 4 patient presented grade II (26.6%), 5 patients presented grade III (33.3%), and 6 grade IV (40%). At the end of laser application, 4 patients showed grade 0 (26.6%), 3 patients presented grade I (20%), 3 patients showed grade II (20%), 4 had grade III (26.6%) and 1 had grade IV (6.7%). The clinical grade IV was reduced in (83.3%) of the cases, grade III was reduced in (20%), and (25%) reduction in grade II. The decrease in grades IV, III and II was associated with an increase in mucositis grade 0 and I.

However in the control group, 5 patients showed grade II (33.3%), 4 patients with grade III (26.6%), and 6 had grade IV (40%) as shown in fig. (2).

After placebo treatment of this group, 2 patients showed grade II (13.3%), 4 patients grade III (26.6%), and 9 had grade IV (60%). The grade IV was increased by (50%) in comparison to pre-placebo treatment scoring.

B- Culture

Group (A): The pre-application of LLLT culture developed growth organisms in 12 cases (80%) and 3 cases (20%) showed no growth.

After the completion of 14 sessions of LLLT, there were 5 cases (33.3%) developed...
growth organisms and 10 cases (66.6%) showed no growth.

Group (B): The pre-application of LLLT culture developed growth organisms in 11 cases (73%) and 3 cases (26.6%) showed no growth.

After the completion of 14 sessions of placebo LLLT, there were 13 cases (86.6%) developed growth organisms and 2 cases (13.3%) showed no growth as in table (3).

Table (3): shows the number and percentage of growth and no growth organisms at the culture swabs in both groups (A and B).

<table>
<thead>
<tr>
<th>Culture</th>
<th>Group (A)</th>
<th>Group (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Growth</td>
<td>12 (80%)</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>No growth</td>
<td>3 (20%)</td>
<td>10 (66.6%)</td>
</tr>
</tbody>
</table>

Fig. (3): Shows the percentage of growth and no growth of organisms pre-application of LLLT in group (A).

Fig. (4): Shows the percentage of growth and no growth of organisms post-application of LLLT in group (A).
Fig. (5): Shows the percentage of growth and no growth of organisms pre-application of placebo LLLT in group (A).

Fig. (6): Shows the percentage of growth and no growth of organisms post-application of placebo LLLT in group (A).

DISCUSSION

Oral mucositis is a common complication of some malignancies treatment, causing therapeutic modifications due to the patient's debilitation which interferes with the prognosis of the disease. LLLT has been used in the treatment of many medical conditions including wound repair processes, musculoskeletal complications and pain control. Clinical studies have shown low energy laser to be effective as analgesics and to accelerate wound healing. This study was conducted to evaluate its efficacy on chemotherapy-induced oral mucositis.

Physical approaches like cryotherapy, low energy Helium-Neon laser or the use of modern radiotherapy techniques with the exclusion of the oral cavity from radiation fields have been shown to be efficacious in preventing mucositis onset. Nevertheless a consensus protocol of prophylaxis and treatment of oral mucositis has not yet been obtained.

The data obtained in this study presented an improvement of the oral status at the end of laser applications both functional and clinical. The functional grade III (cannot eat solids or liquids) was reduced in (60%) of the cases which showed this grade at the starting of the treatment. Also functional grade IV was reduced in (33.3%). The clinical mucositis grade IV was reduced in (83.3%) of the cases, grade III was reduced in 20%, and 25% reduction in grade II. The decrease in grades
IV, III and II was associated with an increase in mucositis grade 0 and I.

The results showed that laser application was effective in reducing oral mucositis after chemotherapy. The possible mechanism may be due to the anti-inflammatory and analgesic effect of the laser on the local tissue, which in turn increase vascularity and re-epithelization of injured tissue. In oral tissues the laser applications could stimulate DNA synthesis in myofibroblasts without degenerative changes and could transform fibroblasts into myofibroblasts which may promote and activate the epithelial healing of mucosa. The results of this study was in agreement with Barasch et al. (1995) who reported that LLLT was effective in treating OM and shortened the period needed for healing (6 days instead of 16 days) when compared to control group. Furthermore, Bensadoun, et al. (2006) concluded that LLLT had a beneficial effect a preventive and curative form for OM when applied on patients with head and neck cancer receiving radiotherapy with percentage of incidence 7.6% versus 35.2% in the group received placebo LLLT. In addition, Cowen, et al. (1997) found that LLLT showed a 33% reduction of severe mucositis in patients during conditioning regimen for bone marrow transplantation (BMT).

The clinical effects of laser therapy on the prevention and reduction of oral mucositis in patients who underwent hematopoietic stem cell transplantation (HSCT) were delaying the appearance of OM up to 6 days versus 4 days in the control group. In the same time LLLT accelerate the healing rate of OM at the day 14 in the study group compared to day 25 in the control group.

Cruz et al. (2007) reported that the LLLT appears to be a simple, non-traumatic technique for the prevention and treatment of radiation induced mucositis. This study showed no evidence of benefit from the prophylactic use of low-energy laser in children and adolescents with cancer treated with chemotherapy when optimal dental and oral care was provided.

The low-level He-Ne laser therapy during the radiotherapy treatment was found to be effective in preventing and treating the mucositis in head and neck cancer patients. Further studies need to be done on a larger sample to find the mechanism.

In contrast, Lara et al. (2007) concluded that application of gallium-aluminum-arsenide (GaAIAs) on animal model (rats) of mucositis, showed that GaAIAs was not effective in comparison to topical dexamethasone.

Despite the use of preventive LLLT, a high incidence of ulcers were still observed in many randomized studies. One study by Barasch et al. (1995) who applied continuous laser illumination with a 632.8 nm wavelength, 25 mW of power and 1 Jcm2 from day -1 to day +3. It was noted that, 20 patients participated served as their own control since the randomization was done between the right and left of the buccal mucosa.
Cowen et al. (1997) applied continuous laser illumination with a 632.8-nm wavelength, 25 mW of power, and 1.5 J/cm² of energy density, from day −5 to −1, to 30 patients. But in the current study a higher energy density (2 J/cm²), a longer wavelength (660 nm) and a higher power (25 mW), in addition to longer length of administration (from day +1 until day + 14) were applied.

Furthermore, Migliorati et al., 2001 applied continuous laser illumination with a 780-nm wavelength, 60 mW of power, and 2 J/cm² of energy density, from day −5 to day +5, to 11 patients and reported that 63.7% of the patients presented with OM grades 3 and 4 (WHO) and 9% of the patients presented with OM grade 2 after HSCT and high-dose chemotherapy.

A randomized clinical trial in which 60 children received LPLT (780 nm wavelength, 60 mW of power, and 4 J/cm² of energy density) for a short period of time (days 1 to 5) showed no difference between LPLT and control groups. It should be noted that the groups treated in that study were heterogeneous; including patients treated with both conditioning and conventional chemotherapy regimens.

In the current study, cultures were made to assess the growth or no growth organisms before and after LLLT application revealed that in group (A), 10 cases (66.6%) developed no growth in comparison to group (B), only 2 cases (13.3%). The high percentage of no growth of organisms in the study group compared to control group can be explained through the increase in the immune response with the activation of T-lymphocytes, macrophages and number of mast cells. Stimulation of the immune system means that infected wounds can be cleared more readily. The use of low-level lasers in wound healing has been shown to speed up the healing of leg ulcers and burn wounds; it has also been shown to improve skin-healing capabilities.

Laser improves wound healing of slow-to-heal or non-healing wounds in soft tissues, due to improved tissue oxygenation and nutrition. Laser-induced microbial killing of photosensitized organisms could have clinical applications in the treatment of infected skin lesions, pending in vivo studies.

The obtained results were in agreement with Nussbaum et al. (2002) who concluded that LLLT applied to wounds with wavelength and radiant exposures in the range of 1-20 J/cm² could produce changes in bacterial growth of considerable importance for wound healing. A wavelength 630 nm caused overall effect while 660 nm caused marginal effect of growth. In contrast 905 nm irradiation increased by 27% of S. aureus growth. These findings might be useful as bases for selecting LLLT for infected wounds. In addition, Nussbaum et al. (2003) reported that 810 nm radiation increased E. coli growth which might delay recovery while LLLT showed that bacterial inhibition growth of P. aeruginosa. Furthermore, Segundo, (2002) found that bacterial reduction was significantly higher for laser group (685 nm, 10 mW, for 3 minutes) when compared to chemical and control groups when applied on root canal contaminated with Enterococcus Faecalis.

So, LLLT has different effects on organisms growth according to its wave length and intensity, this is in corresponds to the current results as still some patients in both groups were developing organisms growth. So, for future researches we recommend culture differentiation of organisms.

By the end of this study, we can concluded that LLLT is very effective in the treatment of chemotherapy induced OM but further studies are needed to investigate the
variation in the parameters and types of laser in the treatment of such cases.

In the current study, the wavelength of LLLT which used was 660 nm while Schubert et al. (2007)\textsuperscript{26} used 650 nm wavelength and reported that it was effective in reducing the severity of oral mucositis. LLLT was well-tolerated and no adverse events were noted. So, all of these results were made for further studies to truly establish the efficacy of this mucositis prevention strategy. Future research needs to determine the effects of modification of laser parameters (e.g., wavelength, influence, repetition rate of energy delivery, etc.) on the effectiveness of LLLT to prevent OM.

**REFERENCES**


تأثير الليزر منخفض الشدة في علاج التهاب الغشاء المخاطي المبطن للفم الناتج عن العلاج الكيميائي

في حالات سرطان الثدي لدى السيدات في سن ما بعد انقطاع الدورة الشهرية

يعتبر التهاب الغشاء المخاطي المبطن للفم من المضاعفات الأكثر شيوعا أثناء العلاج الكيميائي لمرض السرطان، و الذي يؤدي إلى تغيير في خطط العلاج ومن ثم يؤثر على تحسن الحالة المرضية. يعتبر الليزر منخفض الشدة من أساليب العلاج الطبيعي الذي فائدة كبيرة في تقليل الالتهابات والقليل من هذه الدراسة تقييم تأثير الليزر منخفض الشدة على التهابات الغشاء المخاطي بالمثابرة عن العلاج الكيميائي. انتشرت هذه الدراسة في حالات 30 سيدة عانت من سرطان الثدي في فترة ما بعد انقطاع الدورة الشهرية وقد خضعن لعملية استئصال الثدي. وقد قسمت عشوائيا إلى مجموعتين متساويتين، مجموعة (أ) تلقين العلاج بالليزر منخفض الشدة لمدة 14 جلسة يوميا بينما مجموعة (ب) تلقين العلاج المميز بالليزر منخفض الشدة وقيمت شدة التهاب الغشاء المخاطي بالفم عن طريق قياس المواصفات الأكلينيكية والوظيفية الناتجة عن تلك الالتهابات. وقد أظهرت النتائج أن التهاب الغشاء المخاطي المبطن للقسم المعمد على الليزر المنخفض الشدة معد أنه原谅ت بنسبة 60% و 83.3% في المجموعة (أ) في مقابل 20% و 50% في المجموعة الضابطة (ب) بالمقابل بالنسبة لقياس المواصفات الأكلينيكية فقد أظهرت المجموعة (أ) انخفاض في الدرجة الثالثة والرابعة بنسبة 20% و 33.3% في مقابل 50% ارتفاع في الدرجة الرابعة بالمجموعة (ب) وبالتالي نستنتج أن الليزر منخفض الشدة وسيلة آمنة وفعالة وسهل الاستخدام في علاج مثل تلك الحالات.

الكلمات الدالة: الليزر، التهاب الغشاء المخاطي المبطن للفم، العلاج الكيميائي، سرطان الثدي.