Low Level Laser Therapy in oral mucositis: a pilot study

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Abstract

AIM: The goal of this pilot study was to investigate the capacity of pain relief and wound healing of low level laser therapy (LLLT) in chemotherapy-induced oral mucositis (OM) in a paediatric oncology population group. STUDY **DESIGN AND METHODS:** 16 children (mean age 9.4 years) from the university hospital – department paediatric oncology/haematology, suffering from chemotherapy-induced OM were selected. During clinical investigation, the OM grade was assessed using the WHO classification. All children were treated using a GaAlAs diode laser with 830 nm wavelengths and a potency of 150 mW. The energy released was adapted according to the severity of the OM lesions. The same protocol was repeated every 48 hrs until healing of each lesion occurred. Subjective pain was monitored before and immediately after treatment by an appropriate pain scale and functional impairment was recorded. At each visit, related blood cell counts were recorded. **RESULTS:** After 12 mths, records were evaluated and information about treatment sequence, treatment sessions and frequencies related to the pain sensation and comfort were registered. Immediately after beaming the OM, pain relief was noticed. Depending on the severity of OM, on average, 2.5 treatments per lesion in a period of 1 week were sufficient to heal a mucositis lesion. **CONCLUSIONS:** LLLT, one of the most recent and promising treatment therapies, has been shown to reduce the severity and duration of mucositis and to relieve pain significantly. In the present study similar effects were obtained with the GaAlAs 830nm diode laser. It became clear that using the latter diode device, new guidelines could be developed as a function of the WHO-OM grades i.e. the lower the grade, the less energy needed. Immediate pain relief and improved wound healing resolved functional impairment that was obtained in all cases.

Introduction

The most important side effects of oncologic therapy are ulcerations, alopecia, thrombocytopenia, neutropenia and oropharyngeal mucositis (OM). The prevalence of OM in children with cancer occurs between 52% and 80% [Kuhn et al., 2009]. OM, known as most painful oral lesions, requires narcotic analgesia and will give rise to a significant reduction in quality of life [Elting et al., 2008]. Because of the neutropenic condition of these patients, bacterial colonization of these ulcerated lesions may lead to septicemia. Moreover, this complication significantly affects the oncology treatment planning with delays in implementation, dose reduction or even discontinuation of treatment that may influence the oncologic treatment response [Shubert et al., 2007].

Important factors playing a role in the development of OM are:

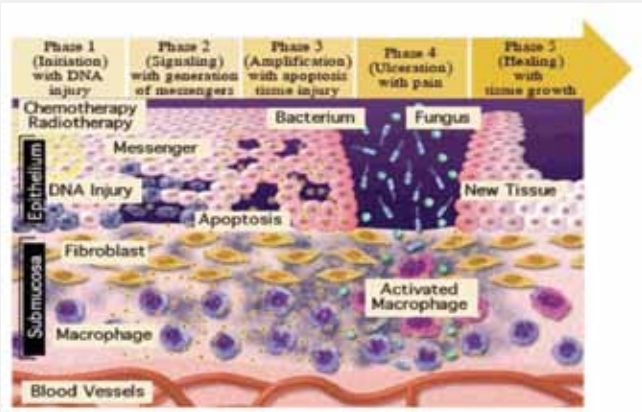
- chemotherapeutic regimen,
- type of malignancy,
- patient's age,
- neutrophil counts,
- use of oral care measures.

Poor oral hygiene, pre-existing mouth damage, impaired immune status and high levels of pro-inflammatory cytokines predispose patients to severe OM [Kuhn et al., 2009]. Ulceration is the major event associated with OM. The non-keratinized surfaces of the oral mucosa, lateral tongue and floor of the mouth are the most frequently involved surfaces. Clinical symptoms appear very soon following radiotherapy in head and neck cancer or within 7 days after initiation of chemotherapy, peaking on days 11 to 14. Healing begins 9 to 14 days after the first clinical signs.

The initial erythaema and atrophy progress to fibrin pseudomembranous exudates covering the ulcerations [Sonis, 2007]. Few direct measures exist to prevent the development or to promote healing of mucositis lesions. Good oral hygiene has an important impact on further development and care generally consists of vigorous mouth cleansing and is aimed at symptom control until immune function recovers [Chen et al., 2004]. Other preventive or therapeutic approaches have been mainly empiric covering a wide variety such as analgesics and local analgesics, cryotherapy, antibiotics, anti-inflammatory agents, growth factors and biologic mucosal protectants. More recently, the successful development of a recombinant human keratinocyte growth factor (KGF-1, palifermin) significantly reduces the severity and duration of severe OM. Palifermin stimulates proliferation and modifies differentiation in epithelial cells, including those of the oral mucosa [Sonis, 2007]. However, in a previous study, 63% of the patients receiving palifermin still developed severe OM, indicating the need for additional treatment procedures [Shubert et al., 2007]. More recently, low-level laser therapy has been accepted as a valuable treatment option for OM by the MASCC (Multinational Association of Supportive Care in Cancer) and ISOO (International Society for Oral Oncology) [Keefe et al., 2007]. This survey herein deals with the use of the low level laser as a supplementary option in treating chemotherapy induced OM in children.

Pathobiology of OM. Mucositis is not a simply cytotoxic damage to the epithelium but has to be seen as a multistep process. It occurs very quickly and simultaneously in all tissues especially in the non-keratinized tissues. According to Sonis [2009], OM can be arbitrarily divided into 5 phases (Figure 1):

Figure 1. *Pathobiology of mucositis, adapted from Soni [2007], Nat Rev Cancer [2004].*



1st phase: the initiation stage; radiation and chemotherapy directly and immediately injure DNA and cause strands to break resulting in clonogenic death of basal epithelial cells. Reactive oxygen species (ROS), a natural byproduct of normal metabolism, from which levels increase dramatically during environmental stress such as radiation or chemotherapy administration, directly damages cells, tissues and blood vessels in the submucosa

2nd phase: the primary damage response (messaging and signaling); transcription factors are further activated by chemo/radiotherapy and ROS ending in up-regulation of many genes which results in production of pro-inflammatory cytokines, leading to further damage, including apoptosis of cells within the submucosa, basal epithelium and micro-circulation.

3rd phase: the amplification stage, the consequence of mediators released in response to the initial insult is a cascade of chain reactions amplifying and prolonging tissue injury. Because the damaging events are focused in the submucosa and basal epithelium, the clinical appearance of the mucosal surface remains normal.

4th phase: the ulceration stage; finally the loss of mucosal integrity produces extremely painful lesions. Ulcers become portals of entry for bacteria, viruses and fungi invading submucosal vessels and causing sepsis in neutropenic patients that stimulates infiltrating macrophages to release additional pro-inflammatory cytokines.

5th phase: healing, this starts with a signal from the extracellular matrix provoking epithelial proliferation, differentiation and migration. Furthermore, a re-establishment of the local microbial flora occurs. Initially there is a lag between the damage at the molecular and cellular level and its clinical manifestations.

Methods and Case Reports

The study comprised 16 young patients from the university hospital, paediatric clinic – department oncology/haematology. The mean age was 9.4 years and gender was equally distributed. Most of them were diagnosed with leukemia and lymphoma (n=12), others were treated for neuroblastoma (n=1), osteosarcoma (n=1), Ewing's sarcoma (n=1) or germ cell tumor (n=1). These patients, receiving chemotherapy, were eligible for the study as soon as they developed OM. All children received the visit of a paediatric dentist for routine odontologic assessment during the intake examination.

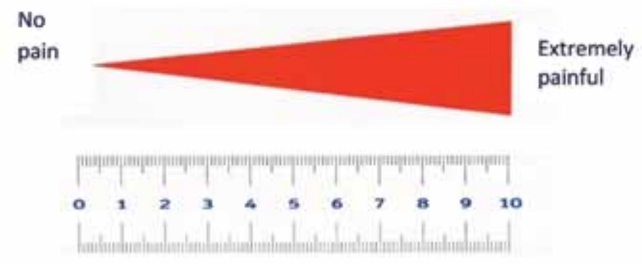
General oral hygiene instructions, supported by an oral care protocol brochure, were given. The use of a soft toothbrush and neutral non-irritating toothpaste after every meal followed by a 0.05% chlorhexidine mouth rinse on an alcohol-free basis twice a day were recommended. Oral assessment was rigorously executed to identify potential sites of infection in the mouth. Dental treatment was planned for restoration or removal of septic teeth as needed,

Laser equipment and patient response. A diode GaAlAs laser, with a continuous wavelength (λ) 830 nm (infrared) and an output of 150mW, was used in this trial. Treatment time (t) for each application point is given by the equation: t (sec) = energy (J/cm²) x surface area (cm²)/power (W). This means that the longer the irradiation is used for the greater the energy is released. This laser belongs to the class 3-B for safety measure, which means that the direct beam is dangerous for exposed eyes but are not hazardous for diffuse reflections. As a protective measure, the patient is asked to wear appropriate goggles that are effective in the 800-850 nm wavelength spectrum.

Patients were assessed for response to laser therapy according to standardized mucositis grading criteria by evaluating development of lesions and time needed for healing. The impact of laser therapy on pain control was evaluated using a visual analogue scale (Figures 2 and 3).

Figure 2. *Modified Faces Pain Scale (derived from the comfort scale of Bieri et al., 1990).*

Figure 3. *The Visual Analogue Scale (both sides).*



Procedure and data collection. The treatment started with a clinical investigation of the lips and oral mucosa. Despite the oral examination at intake, for each visit, possible irritating factors responsible for lesions were assessed. Scoring of OM was executed based on the WHO Oral Toxicity Scale as shown in Table 1. This scale is based on subjective, objective and functional outcomes. Scoring of the mucositis grade per site was executed at every visit. Only the highest score was read per site involved. A questionnaire concerning oral functions, nutrition, speech and deglutition, is of help to assess the grade of mucositis.

Table 1. *Interpretation of the mucositis grade based on the WHO Oral Toxicity Scale.*

Grade OM	Clinical symptoms	Subjective pain sensation	Diet
Grade 0	No symptoms		
Grade 1	Erythema	Sensible	
Grade 2	Ulcerations with/without erythema	Pain	Can swallow a solid diet
Grade 3	Confluent ulcerations with/without exudates	Very painful	Able to swallow liquids but not a solid diet
Grade 4	Deep ulcerations and/or necrosis	Extremely painful	Alimentation is no longer possible

Functional impairment was also recorded in order to control influences from the treatment. Blood cell counts of the platelets and absolute neutrophilic count (ANC) were registered on each laser treatment day. The serum level of the latter was used to compare the progression in healing of mucositis. Prior to and immediately after laser treatment, a pain evaluation was recorded using an age adapted pain scale. For children younger than 9 years-old, the Modified Faces Pain Scale was used and the Visual Analogue Scale (VAS) for the older children (Figures 2 and 3). For each grade of OM a well-chosen energy was released. Grade 1, 2, 3 and 4 OM received respectively 2, 4, 8 and 16 Joule/cm² (Table 2). No contact was made with the ulcerated mucosa and when possible, sometimes the child was asked to assist in retracting the lip or the tongue. Asking for co-operation of the patient gave the child a lot of confidence.

Table 2. *Low Level Laser Treatment (LLLT) guidelines (Diobeam 830nm) as a function of the WHO Oral Toxicity Scale.*

WHO Oral Toxicity Scale	Energy J/cm²
Grade 0	
Grade 1	2
Grade 2	4
Grade 3	8
Grade 4	16

The laser therapy was applied every 48 hrs, repeating the procedure at each visit until complete healing of the lesion occurred. Finally, at the end of each OM episode, the sum of the released energy and the treatment frequency was collected. One OM episode was defined as one period from start of OM development until complete healing of the particular lesion. At each visit, a clear progress in healing was observed. This observation could be achieved because of clinical photographs taken at each visit and at the newly scored OM grade.

Results

There were 16 children treated with LLLT. Some patients suffered from more than one episode of OM and 50 OM episodes were assessed. During those episodes the patients suffered from different grades of lesions; 18% were diagnosed with grade 1, 32% grade 2, 42% grade 3 and 8% suffered from the most debilitating form grade 4. The buccal mucosa (51%) was most frequently affected, followed by lips (19%), tongue (10%), sublingual mucosa (5%) and the palate (4%). Finally other sites (11%) as the gingiva, uvula or oropharyngeal zone were also involved (Figure 4). From Figure 5, illustrating the measurable pain scores (in 28 sessions), it can be seen that with exception of 1 patient, an important immediate pain relief was recorded after laser treatment.

Figure 4. *Frequency of OM involvement per site in a study of 16 Belgian children undergoing chemotherapy for cancer.*

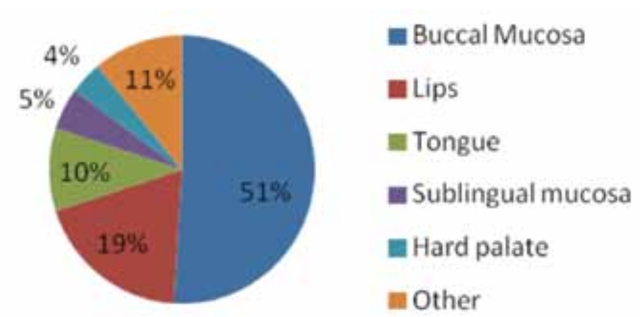
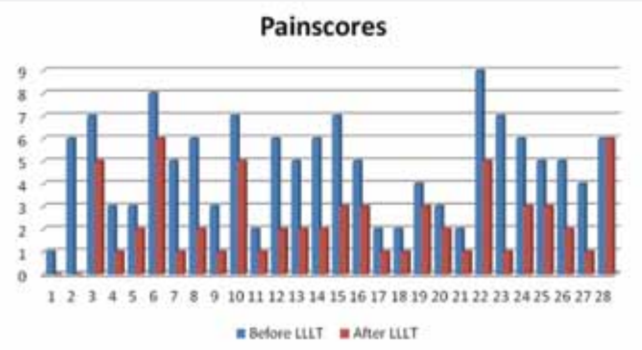


Figure 5. Pain scores before and immediately after one LLLT-session (in 28 sessions).

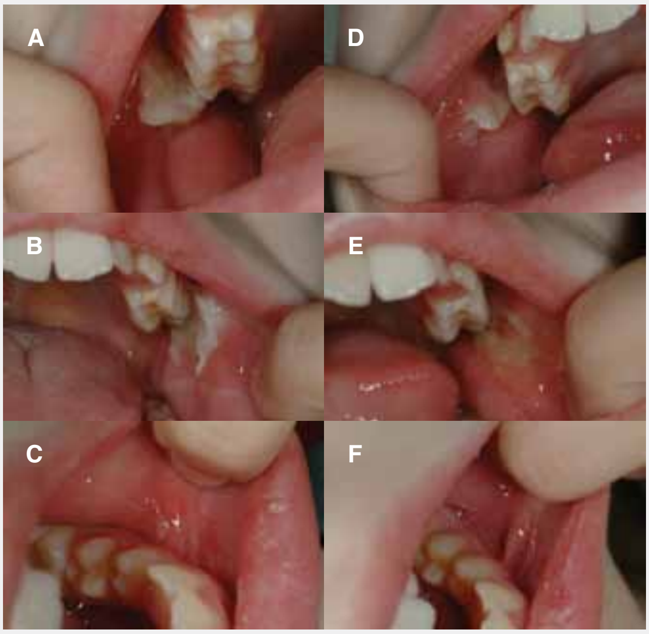


At the next visit, the new initial pain score corresponded to the final (lowest) score from the visit two days before. At each subsequent visit, a clear progress in healing was observed. Some children needed only one laser therapy session, while others needed 6. The number of sessions depended on the severity of OM at the start of the episode; the more severe the OM grade, the more sessions needed. According to the experienced staff, it was noticed that pain relief, healing and better oral functions were related to the laser treatment, even in cases of temporary stagnated neutropenia. Depending on the severity of OM, a mean of 2.5 visits per episode could be realized. All patients tolerated the laser treatment without any adverse effect or reactions.

Case report

A 10 year-old girl suffering from osteosarcoma underwent chemotherapy prior to the surgical removal of the tumour. She was admitted to the hospital and diagnosed with a grade 3 OM on the right and left maxillary buccal mucosa (Figure 6 a, b). On the left mandibular side, a small grade 2 OM lesion is seen (Figure 6 c). On the VAS painscale she scored respectively 7 and 2. She was unable to eat solid food and experienced difficulties in speaking and swallowing. The ANC was 4840/µl. LLLT was administrated respectively 8 and 4 J/cm². Immediately after the treatment a lower painscore was recorded indicating respectively 2 and 1 on the VAS. Only one day later, a spectacular healing of the lesions was seen, recording OM grade 2 on the buccal mucosa (Figure 6 d, e) while the small mandibular lesion disappeared completely (Figure 6 f). Meanwhile, nutrition became possible again, speaking and swallowing was not hindered anymore. Again the lesions were treated but now with an energy corresponding to the new OM grade respectively 4 and 1 J/cm². The painscore decreased from 2 to 0 for the buccal mucosa and remained 0 in the mandibular fold. Nevertheless, the ANC decreased to 2430/µl.

*Figure 6. Intra-oral photographs showing oral mucositis lesions (arrow) before LLLT (**a,b,c**) and 1 day after LLLT (**d,e,f**).*



Discussion

In this report, low-level laser therapy was used in paediatric patients with cancer for the management of chemotherapy-induced OM, supplementary to basic oral health. The prevalence of mucositis, which is a complex process that begins before patients feel pain, can be reduced by good oral hygiene. Ideally, all newly diagnosed children with cancer should have an oral assessment prior to the initiation of chemotherapy [Kuhn et al., 2009]. Poor oral hygiene, pre-existing oral damage, impaired immune status and high levels of pro-inflammatory cytokines predispose patients to the development of severe OM. Chen et al. [2004] found out that oral hygiene care regimens significantly improved oral assessment among patients, reducing the severity of mucositis. The latter was commented on by McGuire et al. [2006] as not conclusive because of the weak research design of the study.

On the other hand, pain from mucositis, neutropenia and thrombocytopaenia may decrease the ability to provide adequate oral care that may increase ulceration and infection further [Chen et al., 2004]. Prevention of ulceration can minimize pain, risk of infection, use of feeding tubes and length of hospital stays. In granulopaenic patients, there is a risk that intact bacteria may invade submucosal vessels to produce bacteremia or sepsis. No standard therapy is known for OM and if therapy exists it is mostly supportive; basic oral care, bland oral rinses, analgesics, cryotherapy, antibiotics, growth factors and cytokines, biologic mucosal protectants and anti-inflammatory agents [Shubert et al., 2007; Kuhn et al., 2009]. More recently, a successful development of a human keratinocyte growth factor, KGF-1 (palifermin), significantly reduced the severity and duration of OM. Nevertheless, some side-effects such as taste disturbances, pain, fever, local or allergic reactions are seen. According to Shubert et al. [2007] 63% still developed severe mucositis. Considerable research has been accomplished and still there is need for other treatment modalities.

Low-level laser therapy (LLLT) has been described as another alternative in management of OM. LLLT is known to relieve pain, having an anti-inflammatory effect and the property to enhance wound healing. The mechanism by which LLLT affects cells is not well understood yet but it seems to be based on bio-stimulation [Parker 2007]. It is believed that low-level laser radiation is absorbed by intracellular photoreceptors in the membrane of the mitochondria. The stimulatory effects are various but the most important are stimulation of β-endorphins and bradykinins, inhibition of production of prostaglandins and interleukins and last but not least an increased cellular activity and angiogenesis is seen. These reactions and stimulatory actions result in analgesic, anti-inflammatory effects and better wound healing [Gao and Xing, 2009].

Nevertheless, the therapy is recommended by the Multinational Association for Supportive Care in Cancer (MASCC)/ International Society for Oral Oncology (ISOO) mucositis study group. In their original guidelines the panel suggested the use of LLLT to reduce the incidence of OM and its associated pain in patients receiving high-dose chemotherapy or chemo-radiotherapy before haematopoietic stem cell transplantation (HSCT). Because of inter-operator variability, clinical trials are difficult to conduct, and their results are not easy to compare; nevertheless, the panel was encouraged by the accumulated evidence in support of LLLT [Keefe et al., 2007]. Nevertheless, the variation of low level lasers with the corresponding wavelength and the diverse mycosis's–grading tools used in laser application studies make standardization of these protocols difficult for their use. The specific parameters of laser therapy that can affect biological response include: 1. wavelength (nm); 2. laser power (mW); 3. amount of energy to be delivered to tissues per surface area (J/cm²), and 4. rate of energy (intensity) [Walsh et al., 2006].

To transfer information objectively and describing the mucositis, the World Health Organization scale (WHO-scale) was used in the present study. The importance of a scale is to describe as precisely as possible, to classify objectively and to measure reproducibly the severity of OM including the patient's functional capabilities. The WHO scale correlates closely with pain scores and functional impairment. Besides the well-known use of this scale [Maiya et al., 2006; Jaguar et al., 2007; Antunes et al., 2008], other investigators assessed the OM grade using the European Organization for Research of Cancer Scale (EORTC) [Genot et al. 2008; Arora et al., 2008] or the National Cancer Institute's Common Toxicity Criteria Scale [Abramoff et al., 2008; Kuhn et al., 2009]. The importance of a scale is to describe as precisely as possible, to classify objectively and to measure reproducibly the severity of OM including the patient's functional capabilities.

From two comparable studies dealing with paediatric oncology patients [Abramoff et al., 2008; Kuhn et al., 2009], only one showed a similar distribution of patients as the present study regarding age and pathology, but carrying out another study design [Kuhn et al., 2009]. In the latter an equal distribution of affected sites is seen as in the present study i.e. the buccal mucosa, the lips and tongue.

Little consistency between the studies exists relative to the specific parameters of LLLT including wavelength, power, energy density, total energy delivered and timing of treatments. Some authors compared the results of the laser therapy with a sham or control group [Shubert et al., 2007; Arora et al., 2008; Abramoff et al., 2008; Antunes et al., 2008; Kuhn et al., 2009], others compared different wavelengths or lasers (diode laser 650nm-830nm versus He-Ne laser 632nm) [Bensadoun et al., 1999; Shubert et al., 2007; Genot et al., 2008;]. Some studies were divided into a preventive and a curative approach [Wong and Wilder-Smit 2002; Shubert et al., 2007; Genot et al., 2008;]. The frequency of treatment differed from daily [Nes and Posso 2005; Shubert et al., 2007], through 3 times a week [Genot et al., 2008], to once a week [Wong and Wilder-Smit 2002; Arora et al., 2008].

The energy released has ranged from 0.7-0.8 J/cm² [Wong and Wilder-Smit 2002], 1.8 J/cm² [Maiya et al., 2006; Arora et al., 2008], 2 J/cm² [Shubert et al., 2007; Genot et al., 2008; Abramoff et al., 2008], 2.5 J/cm² [Jaguar et al., 2007], 4 J/cm² [Kuhn et al., 2009], to 8 J/cm² [Antunes et al., 2008] depending on the wavelength and the property of the laser. In the present study however, the energy released was adapted according to the OM grade that is a unique and new approach.

Despite the differences in type of laser, wavelength or frequency of treatment, all studies had similar results. Studies investigating the preventive capacity of the low level laser confirmed the effectiveness of prophylactic effect. Regarding the preventive capacity of the laser therapy, the incidence of OM seemed to be significantly reduced [Wong and Wilder-Smit 2002; Shubert et al., 2007; Genot et al., 2008]. Curatively, the LLLT was shown to not only be able to reduce oral pain but also the severity and duration of OM [Bensadoun et al., 1999; Maiya et al., 2006; Arora et al., 2008; Antunes et al., 2008; Kuhn et al., 2009].

In agreement with other studies, the reduction in pain found in this study was the most remarkable effect reported. This prompt alleviation allowed patients to improve their eating and hence nourishment which influenced their daily quality of life. Moreover, the improvement in subjective symptoms for impairment of function could directly be credited to the non-progression of the OM. According to Jaguar et al. [2007]

decreasing the duration of OM significantly reduced the time of oral pain and decreased the consumption of morphine.

Conclusion

The three main effects applicable to LLLT are: 1) an immediate analgesic effect, 2) an anti-inflammatory impact and 3) a faster wound healing. Based on these properties and to the results of other studies it can be concluded that in the present study these objectives were obtained with the GaAlAs 830 nm diode laser. In spite of the small patient sample, it became clear that using the latter diode device, new guidelines could be developed as a function of the WHO-OM grades, i.e. the lower the OM grade, the less energy needed. Supported by the WHO mucositis scale, based on both objective and subjective symptoms, healing of the lesions was observed within 1 week. A more extended study is needed to further confirm this promising result.

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