LOW LEVEL LASER THERAPY IN THE PREVENTION AND MANAGEMENT OF ORAL MUCOSITIS INDUCED BY CANCER TREATMENTS: EVIDENCE-BASED DATA FROM RANDOMIZED STUDIES AND META-ANALYSES

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ABSTRACT

We discuss the promising state of the art of Photomedicine for preventative and therapeutic usage in Oral Mucositis (OM) due to cancer therapy.

Recent findings: Photomedicine using LLLT or LED is very effective with intra-oral and extra-oral devices in the management of OM, based on several reports including randomised control studies. A systematic review identified 33 relevant articles which were subjected to meta-analysis based on which laser parameters in routine practice are being defined. Meta-analysis showed that LLLT reduced risk of OM with relative risk (RR) 2.45 (CI 1.85-3.18), reduced duration, severity of OM and reduced number of days with OM (4.38 days, p=0.0009). Relative risk was similar between the red (630-670 nm) and infrared (780-830 nm) LLLT. Pain-relieving effect based on the Cohen scale was at 1.22 (CI 0.19-2.25).

Conclusion: There is moderate to strong evidence in favour of Photomedicine at optimal doses as a safe, relatively inexpensive intervention for cancer therapy-induced OM. It is envisaged that Photomedicine will soon become part of routine oral supportive care in cancer.
Oral Mucositis (OM)

Low Level Laser Therapy (LLLT) was reported effective in reducing the severity of cancer-therapy induced OM lesions in a non-randomized trial initiated in Nice, France, in 1992 [1, 2]. In the recent decade there has been considerable interest into performing clinical LLLT trials in cancer therapy-induced OM, both pilot studies [3-6], and randomized controlled studies [7-17]. All these studies but one confirmed the efficacy of LLLT in the prevention of cancer therapy-induced OM, especially a reduction in high grade OM, duration and delayed onset of OM and associated oral pain.

Current Recommendations on LLLT for OM

Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) guidelines of 2004 on cancer supportive care and management reported LLLT as a “possible option” with a mention on the expensive nature of the commercially available devices requiring specialized training due to variations in laser products, procedures and doses [9, 18]. In 2007, MASCC-ISO ‘evidence-based’ mucositis guidelines have upgraded LLLT as a "recommended" method for the prevention of OM during bone-marrow transplantation or HSCT [18]. An international authority in this field, World Association for Laser Therapy (WALT) has existing guidelines in the treatment doses for LLLT for inflammatory conditions and diseases but not specific to OM. American Cancer Society mentioning the evidence behind LLLT as ‘promising’, but with conflicting evidence on large operator and cost variability.

Outcome of our literature review and meta-analysis

In this perspective, we initiated a systematic review of the clinical evidence with meta-analyses of the use of LLLT to prevent (prophylactic) and treat (therapeutic) OM in cancer patients, to identify possible factors affecting, optimal doses, devices and procedures [19]. Systematic reviews of this nature have been extremely important in reaching consensus and useful in proposing guidelines as it is evident from WALT [20-24]. For example, the trial compliance with WALT guidelines for tendinopathies predicting a positive treatment outcome in 92% from the reported studies [22, 23, 25].

There were 33 potentially relevant papers on LLLT out of which nine were reviews, six case studies and three were animal studies. Three controlled studies were excluded for lack of randomization, while one study lacked a placebo-control group [19]. The final sample consisted of 11 randomized placebo-controlled trials published from 1997 until 2009 with a total of 415 patients [7-17]. The assessors gave similar grading for all the included studies, and a consensus meeting was not needed. Methodological quality was high for the included studies with a mean score of 4.10 (SD +/- 0.74). The following is a concise summary of the literature search which was published in detail elsewhere [19]. The insight acquired from the results that would clearly have direct relevance on a day to day application of LLLT in OM and future of LLLT in medical therapeutics at large.
1) LLLT in the prevention, duration and severity of OM during cancer therapy

It is well known that, OM is inevitable in certain cancer therapy and the underlying pathophysiology being hypothesized mostly based on primate studies. The sole purpose of LLLT is topical, to eliminate the local effects of either RT or chemotherapy in the orofacial region. Eight studies presented categorical data for the risk of developing OM during or after cancer therapy. There was a significant effect in favour of LLLT with a relative risk at 2.45 (95% CI: 1.85 to 3.18) for prevention of OM in conjunction with cancer therapy. However, the analysis revealed significant heterogeneity ($I^2=54\%,$ $p=0.03$) between trials. An analysis of irradiation parameters revealed that one study deviated from the others by giving a considerably lower dose (0.18 Joules/cm$^2$) and shorter irradiation time (3s) than the other studies [12]. After sub-grouping this trial in a separate category, heterogeneity was no longer present ($I^2=16\%,$ $p=0.31$) and the relative risk improved to 2.86 with a narrow confidence interval (95%CI: 2.15 to 3.82).

Duration of OM, especially in higher grades is critical since it influence the treatment, duration of hospital stay and to a certain extend predict success of treatment and complications such as graft versus host disease (GVHD) in HSCT. Six studies looked at the effect of duration of OM and LLLT reduced significantly the number of days with OM grade 2 or above with 4.38 days ($p = 0.0004,$ 95%CI: 3.35 to 5.40).

Six trials presented seven different comparisons of continuous data for mucositis severity. As the trials used different mucositis index scales, the combined results were only calculated as the standardized mean difference (SMD). The combined SMD effect size was 1.33 (95% CI: 0.68 to 1.98) and corresponding to a very good effect. However, heterogeneity was present and the reasons for heterogeneity were explored in a separate subgroup analysis of wavelengths without resolving the heterogeneity. A further analysis of wavelength-specific doses revealed that a dose of 2 Joules/cm$^2$ with an infrared wavelength was ineffective (SMD 0.38; 95%CI: -0.19 to 0.96) in reducing mucositis severity, whereas a dose of 6 Joules/cm$^2$ was highly effective with an SMD at 2.17 (95%CI: 1.48 to 2.86) and without signs of heterogeneity between trials ($I^2=0\%$ and $p=0.89$).

2) Wavelength of LLLT and OM

It is critical to find an optimal wavelength of LLLT since the oral mucosa in jeopardy is fragile both physiologically and literally and, an insult of any kind will have devastating consequences such as compromised oral function resulting in deterioration of OM due to functional trauma and subsequent portal of entry of pathogens leading to possible systemic infection. Compromised oral epithelial thickening and increased oral mitotic index are detrimental to the damage that is anticipated while either undergoing a local obliteration of normal cells as in RT of head and neck and also through local infiltration of chemotherapeutic agents giving rise to secondary damage. The subgroup analysis revealed no heterogeneity between trials for the red (630-670nm) and the infrared (780-830nm) subgroups respectively ($p>0.21$ and $I^2<32\%$), and there were no significant wavelength differences in relative risks between red at 2.72 (95% CI: 1.98 to 3.74) and infrared at 3.48 (95%CI: 1.79 to 6.75).

3) Pain-relieving effect of LLLT in OM

Pain is a common complaint in the rather sensitive orofacial region. Severity of pain in OM may depend upon parameters such as pain threshold of individuals, existing oral health, type of treatment, underlying disease and of course the extent and severity of OM. Four trials
reported continuous data on pain intensity from different scales. The combined analysis revealed a significant effect of LLLT with an SMD at 1.22 (95% CI: 0.19 to 2.25), but also significant heterogeneity caused by one trial [16]. This trial differed clinically from the other trials by a considerably longer treatment period of 6 weeks, while the other studies lasted 2-3 weeks. Removal of this study restored homogeneity (I²= 0% and p=0.58), and reduced the effect size to 0.61 but with narrow confidence intervals (95%CI: 0.29 to 0.94).

4) Complications of LLLT in OM

An already compromised patient both systemically and locally in the orofacial region, it is crucial to make sure that any type of therapy would have minimal, if not nil late complications in the form of adverse side effects. All the studies reported possible side-effects, but none found side-effects or adverse effects other than those reported for placebo. On the contrary, vast majority of published trials reported that LLLT was very well tolerated among patients.

Discussion

Our analyses showed that there is scientific evidence indicating narrow confidence intervals from high quality randomized placebo-controlled trials. From this evidence we gather that a fairly simple regimen on prophylaxis and therapeutics can be proposed by strictly following the parameters such as the i) output, ii) dosage, mode of application by site, duration of application per target, duration of total therapy and also most importantly targeting the lesion per sae and finding the right commercially available product for your specific needs.

Our observations from this review relate well to the emerging LLLT evidence in other inflammatory conditions such as rheumatoid arthritis and acute post-operative pain [26]. The optimal clinical doses found in the current review are within the same range as those previously found for rheumatoid arthritis and post-operative pain. It is also interesting to note that the variety of different cancer therapies involved in the included trials did not seem to seriously interfere with the beneficial effects of LLLT. Comparison of LLLT efficacy to other pharmacological agents indicated in controlling OM is outside the scope for this review. In terms of adverse side-effects, LLLT was very well tolerated with hardly any withdrawals due to adverse events, and no serious incidents were reported.

With regard to the different types of LLLT applicators for the head and neck region, we have the option of commercially available extra-oral devices and intra-oral devices (Figure 4); targeting structures such as cutaneous and oral mucosal surfaces, respectively. Also we must remember the fact that, while using an extra-oral device for the application of LLLT, to a certain extent (with wavelengths around 830 nm, not with 630-660 nm), we may be able to indirectly reach intra-oral surfaces such as the oral mucosa, vestibule and inner epithelial surfaces of the lips in a dentate subject. This proves that, a combination of the above two devices must be considered while managing the head and neck RT-induced effects but not necessary in chemotherapy induced intra-oral effects.

Finally, we believe that, the following parameters should become mandatory while considering LLLT in OM. The parameters to be considered include, wavelength (nm), power (mW), Joules/cm² per point (or “dose”), energy density, spot size, power density (mW/cm²), and laser machine calibration. Treatment characteristics should include the total number of
Joules/cm² in any single laser session, the total number of sessions, the frequency of sessions (treatment protraction), the site(s) of treatment, and some precision regarding laser administration (contact pressure treatment, application over single area at one time than scanning motion, preparation of the mucosal or cutaneous surface) and most importantly a well-trained individual such as oral medicine specialist who could assess the orofacial region, lesions and grade them accordingly.

**Figure 1**: Intra-oral laser application
References


