



Low Level Laser Therapy & cancer therapy-induced mucositis

clinical research

Low level laser therapy (LLLT): A new paradigm in the management of cancer therapy-induced mucositis

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E-mail Print Link In this issue of the Journal¹, Maiya et al report their experience with low level laser therapy (LLLT) in the prevention of radiation-induced mucositis, using a He-Ne laser in oral cancer patients.

The results of this study are quite convincing regarding the lack of grade 3 or 4 mucositis observed during patients' survey in the laser group (when knowing the mucositis history of head and neck cancer patients treated with radiation); and only 7 of 25 patients developed grade 2 mucositis during the same period of survey in the laser group. This series of 50 patients is of great interest, confirming previous randomized studies for this type of patients.

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However, for the diffusion of this method, very precise technical data are mandatory. In particular, laser parameters have to be very carefully assessed, with the same precision we find in external radiation therapy for example.

Mucositis is recognized as one of the principal dose limiting factors during radiotherapy and radiochemotherapy for head and neck cancer, and during haematopoietic cell transplant conditioning. What is Mucositis? Pathologic evaluation of mucositis reveals mucosal thinning leading to a shallow ulcer thought to be caused by inflammation and depletion of the epithelial basal layer with subsequent denudation and bacterial infection. The wound healing response to this injury is characterized by inflammatory cell infiltration, interstitial exudate, fibrin and cell debris producing a "pseudomembrane" analogous to the eschar of a superficial skin wound².

"Low" or "low and middle" energy (output power ranged from 5 to 200 mW) irradiation with He/Ne laser (wavelength 632.8 nm) has been reported to be a simple atraumatic technique (with no known toxicity in clinical setting), useful in the treatment of mucositis of various origins. Healing of chronic wounds (skin or ligaments) and activation of post-surgical healing are some other potential indications. Irradiation by LLLT corresponds to a local application of a high photon density monochromatic light source. LLLT effects have been confirmed by numerous in vitro studies, they are influenced by cell type, laser wavelength, and energy dose. Three main effects are suggested for this type of radiation (with adequate energy rate or fluence on the target) : (i) analgesic effect ($\lambda = 630-650$ nm, $\lambda = 780-900$ nm), (ii) anti-inflammatory effect (same wavelengths), and (iii) wound healing effect (proved for He/Ne laser : $\lambda = 632.8$ nm ; and suggested for $\lambda = 780-805$ nm), all assessed by physical, biological, and experimental studies³. The mechanism of action of the healing effect at a molecular and enzymatic level consists mainly of the activation of energy production in mitochondria (ATP). During oncological treatments, detoxification of free radicals and/or reduction of free radicals formation, induced by chemo- and radiotherapy, are complementary effects (currently being studied by several teams). The preventive effect of LLLT raises a lot of interest, but needs more experimental data to be confirmed.

In clinical practice, LLLT (or "soft-laser" therapy) with 25-60 mW He/Ne laser was first reported effective in reducing the severity of oral mucositis lesions in a non-randomized trial, initiated in Nice (France) by Ciais et al in 1985³. Schubert et al from Seattle⁴, identified a trend towards lower oral mucositis scores, on all examination days, in a phase I/II study, in which laser application was performed prophylactically during conditioning before bone marrow transplant. The efficacy of this method in the prevention of chemotherapy induced oral mucositis has been subsequently confirmed by Cowen et al in a prospective, double-blind randomized trial, in patients undergoing bone marrow transplant⁵. In this study, He/Ne laser was administered to the treatment group during conditioning (5 days), prior to the day of transplant. It showed a 33 per cent reduction of grades 3 and 4 mucositis in laser treated patients.

High incidence of radiation-induced mucositis prompted a randomized multicenter trial in France in 1994 to evaluate LLLT for the prevention of acute radiation-induced oropharyngeal mucosal lesions⁶. In this phase III randomized study (testing 60 mW 632.8 nm He/Ne laser), the main objective was to determine whether preventive He/Ne laser beam applications could reduce or prevent oropharyngeal mucositis caused by radiotherapy. Daily oral hygiene (cleaning of the teeth and dental prosthesis) during treatment was recommended. Patients were assigned to either laser treatment (L+) or sham-treatment (L-) by computer blocked randomization. Analgesics were authorized, but not during the 2 days preceding each week evaluation. Laser was delivered to the tissues by a straight optical fiber with a 1.2 mm spot size. The 9 treatment areas, each one being a 1 cm² surface, included : posterior third of buccal mucosa, soft palate and anterior tonsillar pillars. Laser illumination consisted of a continuous beam calibrated at the end of the optical fiber every day. The treatment time (t) for each application point was given by the equation : $t \text{ (sec)} = \frac{\text{energy (J/cm}^2\text{)} \times \text{surface (cm}^2\text{)}}{\text{Power (W)}}$. The average energy density delivered to the treatment areas was 2 J/cm². All laser illuminations were performed by the same individual in each center. This operator was the only person to know whether or not the patient was sham-treated, and did not participate in the evaluation and scoring of mucositis. The

whole irradiation field, the oral cavity and the visible oropharynx were inspected weekly during seven weeks by one specific physician (head and neck surgeon, or radiation oncologist), blinded to the result of randomization. The evaluation and scoring of mucositis and pain was performed on the zone of interest of the study (posterior oropharynx). Criteria for evaluation were the standard WHO scale for mucositis in the oropharynx, and a segmented visual analogic scale for pain (patient self evaluation). In this "radiotherapy" study also, that we had the opportunity to co-ordinate, laser applications delayed the time of onset, attenuated the peak severity and shortened the duration of oral mucositis. Regarding the degree of objective mucositis, the difference between laser treated and non laser treated patients was statistically significant from week 4 to week 7. Results on decrease in pain intensity were also quite convincing. Laser applications reduced the incidence and duration of morphine administration. Ability to swallow was improved.

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