Patients With Moderate Chemotherapy-Induced Mucositis: Pain Therapy Using Low Intensity Lasers

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BACKGROUND: Intensive cancer therapy normally affects malignant and normal cells with high replication rates. Cells in the gastrointestinal tract are therefore commonly affected by cytotoxins. This often results in the development of chemotherapy-induced oral mucositis (COM). COM is the inflammatory response of the oral mucous membrane to the chemotherapy drugs. Low level laser therapy (LLLT) has proved to be effective in treating and repairing biologically damaged tissue and to reduce pain. LLLT has also proven to be an efficient method for the prevention of oral mucositis.

OBJECTIVE: To investigate the effect of LLLT on pain relief among patients who have developed COM.

METHOD: The study was performed as a clinical test with a sample consisting of 13 adult patients receiving oncology treatment. The patients were treated during a 5-day period, and the pain was measured before and after each laser application. The laser used was an AsGaAl, with a wavelength of 830 nm and a potency of 250 mW. The energy given was 35 J cm(-2).

ANALYSIS: The results were analysed using the Wilcoxon test.

RESULTS: There was a significant (P = 0.007) 67% decrease in the daily average experience of pain felt before and after each treatment, confirming that LLLT can relieve pain among patients who have developed COM.

STUDY LIMITATIONS: The low number of COM patients at the hospital did not allow a control group to be included in the study, and therefore the results contain a potential placebo effect.

IMPLICATIONS FOR NURSING CARE: The most important benefit the authors consider to be the value for the patients of better and quicker treatment with a drastic reduction in painful mucositis..

Pilot Study Of Laser Effects On Oral Mucositis In Patients Receiving Chemotherapy

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PURPOSE: The purpose of this study was to examine the effectiveness of laser therapy in the prevention and/or healing of chemotherapy-induced oral mucositis lesions. This study also evaluated the ease and feasibility of the laser therapy and the impact of the treatment on improving the patient's quality of life.

PATIENTS AND METHODS: Fifteen patients with an episode of prior chemotherapy-induced grade 3 or 4 mucositis with 5-fluorouracil continuous infusion consented to participate in this study. All patients were provided with standardized mouth care instructions at the initiation of chemotherapy treatments. Enrolled patients received laser therapy treatments 24 hours before the chemotherapy and then recommenced weekly with evenly distributed exposure to the standardized designated areas by one operator during the entire cycle of chemotherapy at the same doses until the mucositis resolved or the chemotherapy cycle was completed. Intraoralperfusion was measured by laser Doppler technology. Patients were assessed for

response to laser therapy according to standardized mucositis grading criteria by evaluating development of lesions, extent and duration of lesions, and time to healing. The effect of laser therapy on ability to continue planned chemotherapy, the reduction in dose, delays, and ability to maintain planned dose intensity were assessed. The impact of laser therapy on pain control was evaluated using the visual analogue score. A quality-of-life survey was completed by each patient at the initiation of chemotherapy and then weekly throughout the chemotherapy.

RESULTS: Eleven of 15 patients experienced grade 0 mucositis, three patients experienced grade 1 to 2 mucositis, and one patient experienced grade 3 to 4 mucositis. Fourteen patients completed the lasertherapy as planned, and none of the patients withdrew from the laser therapy treatments because of noncompliance. One patient continued to experience grade 4 mucositis that necessitated an interruption in the planned chemotherapy regimen and, consequently, the laser treatment. Patients tolerated the laser therapy very well and did not report any increased discomfort. No significant changes in perfusion were observed as a result of laser therapy.

DISCUSSION: In this pilot study, laser therapy significantly reduced the incidence and the severity of mucositis in chemotherapy patients. The laser therapy does not appear to promote wound healing by affecting the intraoral perfusion, as assessed by Doppler measurements. The mechanisms involved in the mediating of the observed effects remain unknown at this time. Continued research is warranted to determine the optimal laser wavelength and parameters.

HeNe Laser Reduces Mucositis

a) Barasch B et al. **Helium-Neon Laser Effects On Conditioning-Induced Mucositis In Bone Marrow Transplantation Patients**. Cancer. 1995; 76 (12): 2550-2556.

Oral mucositis is a common complication of bone marrow transplantation conditioning therapy. Different drugs are given in order to reduce rejection of the implant. These drugs induce an oral mucosits. The mucositis is painful and complicates nutrition. Sometimes the intake of the drug has to be stopped due to complications. In the study above 20 patients received HeNe to their oral mucosa, either right or left of midline. One side was sham irradiated. Laser treatment was well-tolerated and reduced the severity of oral mucositis.

b) Cowen D et al. **Low energy helium-neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial**. Int J Radiat Oncol Biol Phys. 1997; 38 (4): 697-707.
Significant reduction of oral mucositis using a 60 mW HeNe laser.

Chemotherapy- And Radiotherapy-Induced Mucositis In Head And Neck Cancer Patients: New Trends In Pathophysiology, Prevention And Treatment
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Mucositis is the intensity-limiting toxicity in the management of locally advanced non-resectable head and neck cancer with radiotherapy and chemotherapy. New radiation modalities (hyperfractionation and/or acceleration) as well as combined modality regimens in this situation induce higher rates of acute toxicity. Hyperfractionation, for example, allows higher control rates, with few late toxicities, but it slightly increases acute mucositis. The addition of chemotherapy introduces systemic toxicity and can exacerbate local tissue reactions when used concurrently with radiotherapy. Mucositis is recognized as the principal limiting factor to further treatment intensification. As local regional control and overall survival are related to dose-intensity in this

case, further research into the assessment, analysis, prevention and treatment of mucosal toxicity is not only crucial to improvement in quality of life, but certainly also to improved rates of disease control. Several topical and systemic treatments are directed to the decrease and the acceptance of this acute toxicity, but few have shown a significant preventive effect. The efficacy of low-level laser therapy in the management of such toxicity could hence yield important developments with this method in the field of oncology.

Chemo-And Radiation-Induced Mucositis : Results Of Multicenter Phase Iii Studies
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Considerable buccal toxicity of radiotherapy and/or chemotherapy in patients with cancer can cause patients to become discouraged and can alter their quality of life. In addition, such toxicity often necessitates alterations of treatment planning, with grave consequences in term of tumor response and even survival (concept of dose-intensity). With 5-fluorouracil and head and neck radiotherapy for example, acute mucosal toxic effect is the main limiting factor for which no clinically appropriate prophylaxis or efficacious antidote has been found to date. Management of oral mucositis is currently primarily directed at palliation of the symptoms, and prevention of infections. Low Level Laser Therapy (LLLT) has been reported effective in reducing the severity of oral mucositis lesions in a non-randomized trial, initiated in Nice (France) by Ciais et al. (1).

The efficacy of this method in the prevention of chemotherapy induced oral mucositis has been subsequently confirmed in two prospective, double-blind randomized trials, in patients undergoing bone marrow transplant (2 ; 3). These initial findings and the high incidence of radiation-induced mucositis prompted a randomized multicenter trial to evaluate LLLT for the prevention of acute radiation-induced oropharyngeal mucosal lesions. The trial was open to patients with carcinoma of the oropharynx, hypopharynx and oral cavity being treated by external radiotherapy, with a total dose of 65 Gy at a rate of 1 fraction of 2 Gy/day, 5 days a week, from cobalt-60 or linear accelerator photons, without prior surgery or concomitant chemotherapy. Between September 1994 and March 1998, thirty patients entered this double-blind randomized study conforming to the Huriet law. The goal was to determine whether preventive HeNe laser beam applications could reduce or prevent oropharyngeal mucositis caused by radiotherapy.

Patients characteristics: There were 26 men and 4 women. Mean age was 60.4 years (range 36 - 78). Oral examination and preventive dental management were performed prior to 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. The protocol called for the inclusion of 30 patients, 15 in each arm. No associated anti-inflammatory or other treatment was authorized. Analgesics could be prescribed, but not during the 2 days preceding each week evaluation. Patients received HeNe laser applications daily for five consecutive days (Monday to Friday) each week, during the seven weeks of radiotherapy.

The malignant tumor had to be located outside the areas selected for randomized preventive LLL application. Laser was delivered to the tissues by a straight optical fiber with a 1.2 mm spot size. The 9 treatment areas included : posterior third of buccal mucosa, soft palate and anterior tonsillar pillars. Laser illumination consisted of a continuous beam (wavelength: 632.8 nm; power: 60 mW), calibrated at the end of the optical fiber every day. The treatment time (t) for each application point was given by the equation : t (sec) = energy (J/cm2) x surface (cm2)/ Power (W). The average energy density delivered to the treatment areas was 2 J/cm2, and was applied on these nine points, equally distributed on the treated surfaces, for 33 s per point (each specific LLL session lasted approximately 5 minutes). The 60 mW lasers were designed and produced by Fradama S.A. (Geneva, Switzerland). 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 mucositis. During the

sessions, patients wore wavelength-specific dark glasses and were instructed to keep their eyes closed, to assure that they did not know whether they were sham-treated or whether they received laser applications. The laser made the same noises, and the probe was held in the mouth exactly the same way, when treating control subjects and when treating laser patients. The whole irradiation field, the oral cavity and the visible oropharynx were inspected weekly during seven weeks by the same physician (head and neck surgeon, or radiation oncologist), blinded to the result of randomization.

The evaluation of mucositis and pain was performed on the oropharyngeal areas (9 points). 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 phase III study, no adverse effect was noted with the use of a 60-mW HeNe laser, though it is important to emphasize the importance of preventing retinal damage by the use of wavelength-specific goggles. This is consistent with previous reports. Laser applications delayed time of onset, attenuated the peak severity and shortened the duration of oral mucositis. The difference between L+ and L- patients was statistically significant from week 4 to week 7. With the total delivered dose of 65Gy, conventionally fractionated, all L- patients developed mucositis at week 2, with a peak at week 5 (13 with grade 3 mucositis, and 2 with grade 2 mucositis). All L+ patients also had mucositis at week 2, with a peak at week 5 (5 with grade 3 mucositis, 9 with grade 2, 1 with grade 1). During the 7 weeks of treatment, the mean grade of mucositis in L+ patients was significantly lower ($p=0.01$) than the mean grade in L- patients. Results on decrease in pain intensity were also quite convincing. Laser applications reduced the incidence and duration of morphine administration. Ability to swallow was also improved. These results confirm previous data collected with this method, especially for patients undergoing bone marrow transplant (BMT). In a prospective study, Barasch et al. (2) used a 25- mW laser on one side of the mouth only and reported a statistically significant reduction in oral mucositis on that side, according to the scoring system they used. In the Barasch study, each patient was his or her own control, which could be of importance, since mucosal damage on the sham-treated side could have benefited also from a distant systemic laser effect. Cowen et al. (3), using a 60 mW HeNe laser, performed a double-blind randomized phase III trial, in which laser was administered to the treatment group during conditioning, prior to the day of transplant. This study showed a 33% reduction of grades 3 and 4 mucositis in L+ patients. In this trial, mucositis was scored according to an oral examination guide, with a 16 items scale, of which 4 were assessed by the patients themselves. Daily mucositis index was significantly lower in L+ patients ($p < 0.05$) from d+2 to d+7 after BMT. The duration of grade 3 stomatitis was also reduced in L+ patients ($p = 0.01$). Oral pain was lower ($p = 0.05$), and L+ patients required less morphinomimetics ($p = 0.05$). Finally, xerostomia and ability to swallow were improved among L+ patients ($p = 0.05$, and $p = 0.01$, respectively). All these results were in keeping with previous observations, suggesting the efficacy of the method (1, 4). Schubert et al. for example (4), identified a trend towards lower oral mucositis scores, on all examination days, in an interim results report of a phase I/II study, in which laser application was performed prophylactically during conditioning before BMT. In conclusion, LLLT seems to be a safe and efficient method for the prevention of chemo- and radiation-induced mucositis, with a tremendous potential interest for combined modality treatment. The concomitant use of chemo- and radiotherapy is becoming the new standard of care in advanced head and neck cancer, with very encouraging results, even in nonresectable cases. Since the main limiting factor of these combined protocols is the acute mucositis, this complementary treatment option with low level HeNe laser could be important in enhancing the feasibility of such regimens, and especially in the conservation of dose-intensity effect. At Nice, where the method is now used routinely during head and neck radiation, we project a new study testing LLL in patients being treated with concomitant chemo- and radiotherapy for advanced head and neck cancer. Even more than the improvement of patient comfort, the therapeutic index of combined specific treatment should be increased by the use of LLLT, besides standard supportive care, oral care and enteral nutrition (5). During this study, other laser wavelengths and powers could be tested, and compared to 60-mW HeNe laser.

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