Bone Marrow Transplantation (2003) 32, 1031–1034

www.nature.com/bmt

Case Report

CO_2 laser in oral graft-versus-host disease: a pilot study

S Elad[1], R Or[2], MY Shapira[2], A Haviv[1], D Galili[1], AA Garfunkel[1], M Bitan[2] and E Kaufman[1]

[1]*Oral Medicine Department, The Hebrew University-Hadassah School of Dental Medicine founded by the Alpha Omega Fraternity, Jerusalem, Israel;* [2]*Bone Marrow Transplantation Department, Hadassah University Hospital, Jerusalem, Israel*

Summary:

This paper is the first to report the benefits of CO_2 laser treatment for pain control in severe oral chronic graft-versus-host disease (GVHD). A CO_2 laser device was used during 17 treatment sessions in four patients. The CO_2 laser was applied over the mucosal lesions using 1 W for 2–3 s/1 mm^2. This treatment resulted in a consistent and significant decrease in pain, measured using a standard visual analogue scale. These results suggest that the CO_2 laser can be used for the alleviation of pain in oral chronic GVHD.
Bone Marrow Transplantation (2003) **32,** 1031–1034. doi:10.1038/sj.bmt.1704272
Keywords: oral GVHD; CO_2 laser; pain relief

Following hematopoietic stem cell transplantation (HSCT) a variety of complications, including chronic graft-versus-host disease (GVHD), occur, 25–70% of which involve the oral cavity.[1] These oral lesions can present as painful, erythematous and ulcerative areas.[1] Sites commonly involved include the buccal mucosa as well as the lateral and ventral aspects of the tongue. Mucosal lesions can cause significant pain and increase the risk of oral infection. Sclerodermatous changes can cause perioral fibrosis restricting opening and interfering with oral function.[1,2]

The treatment for GVHD usually involved first and second lines of treatments with systemic steroids, cyclosporine and azathioprine. However, oral GVHD is often refractory to systemic treatment, necessitating complementary topical treatment. Furthermore, when the oral mucosa is the solitary site of GVHD involvement, a topical approach may prevent the severe side effects associated with systemic treatments. There are several agents currently used topically for oral GVHD. These include palliative rinses, topical immunosuppressive agents (such as steroids, cyclosporine and azathioprine[1,3,4]) and phototherapy.[5] Adjunctive treatments include oral hygiene to avert infection and measures to prevent complications of xerostomia (such as topical fluorides, saliva substitutes and sialogogues, that is, pilocarpine).[1]

A low-energy laser was first reported to prevent radiation-induced mucositis in cancer patients.[6] A randomized trial with 30 patients found that the low-energy He/Ne laser is capable of decreasing the severity and duration of oral mucositis associated with radiation therapy as well as reducing patient reports of oral pain.[6] Two recent pilot studies have shown the palliative effects of low-energy laser therapy for oral mucositis.[7,8] In these studies, lasers were operated in the milli-Watt range. The CO_2 laser that we selected allows treatments at higher power (1–10 W range).

The potential of the CO_2 laser as a pain relief modality was initially reported in a small group of patients suffering from recurrent aphthous ulcers.[9] The palliative effects of the CO_2 laser have not been assessed for other mucosal lesions. Therefore, we speculated that the CO_2 laser can ease suffering from inflammatory lesions of oral chronic GVHD. The exact mechanism of the analgesic effect of the CO_2 laser is unknown. A possible explanation for this is that the CO_2-laser-activated c-fibers induce a central somatosensory cortical response.[10] Conflicting evidence suggests that the CO_2 laser induces a spinal inhibitory effect via peripheral nerve stimulation.[11]

The purpose of our pilot study was to evaluate the efficacy of the CO_2 laser to relieve severe pain caused by oral chronic GVHD.

Patients and methods

A total of 17 laser treatments were provided to four HSCT patients (two males, two females) with severe painful oral chronic GVHD. All patients were hospitalized due to GVHD. During days prior to laser treatment, systemic analgesics (morphine and methadone) and local anesthetic mouthwashes (lidocain) were administered according to the severity of oral mucosal pain and patient demand.

The laser device used was an Opus20™ (ESCq/Sharplan/Luxar group, Netanya, Israel), a unique integrated laser system incorporating Er:YAG and CO_2 lasers. The CO_2 laser wavelength in this device is 10.6 μm. After a routine calibration procedure, the Opus20™ was operated using 1 W power with a defocused handpiece for 2–3 s per site in a continuous pulsed manner. At 1 cm distance from the mucosa, the beam diameter was 0.67 mm. The treated mucosa was kept wet during the entire procedure.

Correspondence: Dr S Elad, Oral Medicine Department, The Hebrew University-Hadassah School of Dental Medicine, POB 12272, Jerusalem 91120, Israel.
E-mail: eladhome@md.huji.ac.il
Received 08 January 2003; accepted 15 May 2003

All patients were examined in the Hospital Oral Medicine department before laser therapy. They were requested to grade their oral pain on a 10-grade scale (visual analogue scale (VAS) – while '0' represents no pain, '10' is regarded as the most severe pain possible). Protective measures during laser operation were taken, including protective eyeglasses, care to avoid burning and fire hazards and an appropriate smoke evacuation system. The rooms in which the laser treatments were carried out complied with safety regulations. The CO_2 laser was applied over the mucosal lesions with an operating distance of less than 5 mm. Post operative VAS was obtained by the same examiner as the pre operative VAS immediately after laser treatment. A detailed description of the treated site was recorded. The patient's need for local anesthesia during the CO_2 treatment and systemic analgesics following treatment was documented as an indication of the level of pain or possible adverse reactions to the CO_2 laser treatment. Albumin levels were compared before and several days following treatment and served as an indication of improved nutrition.

Results

The mean age of the four patients was 30.5 years (range 17–46 years). All patients were hospitalized due to deterioration of extensive GVHD, involving the liver, skin and gastrointestinal tract mucosa. A summary of patient characteristics is shown in Table 1.

Following laser treatment as described above, there were no visual effects of damage to the oral mucosa, such as coagulation, vaporization or mild erythema.

Sites and treatment outcome are presented in Table 2. In 14 out of 17 laser treatments, the patients reported immediate post operative relief (82.3%). The VAS values are presented in Table 2. The improvement in VAS immediately post operatively was 40% (a reduction of the VAS score from 8.09 before the treatment to 4.88 immediately after the treatment). The improvement in the VAS score was reported rapidly, not more than 2 min after CO_2 laser treatment. The average VAS score during CO_2 treatment was 3.47, indicating that the laser emission elicited only a minor nociceptive reaction in the oral mucosa. The treatment was consistently successful in all patients (Table 3). No aggravation of oral lesions was noted after laser treatment. None of the patients asked for local anesthesia during laser treatment and there were no requests for analgesics following treatment. In two patients, blood albumin levels returned to the normal range within 12 days of the laser treatment (from 34 to 37 and 29 to 38 g/l). Due to the improved albumin levels (a measure of nutritional status), in one patient total parenteral nutrition

Table 1 Patient characteristics

Patient no.	*Age (years)*	*Sex*	*Indication for HSCT*	*HSCT type*	*Time since HSCT*	*GVHD onset/severity*	*Previous systemic therapy*
1	35	F	ALL (relapse)	Matched	22 mo.; 1 mo.[a]	Progressive/ext.	P, Csp, A, T, MTX, FK506
2	17	M	CLL	Matched, unrelated	9 mo.	Progressive/ext.	P, Csp, A, T, MTX, FK506
3	24	M	NHL	Matched	12 mo.	Progressive/ext.	P, Csp, A, T, MTX
4	46	F	CML	Matched	7 mo.	Progressive/ext.	P, Csp, A, T, MTX

Pt. = patient; mo. = months; ext. = extensive; P = prednisone; Csp = cyclosporine; A = azathioprine; T = thalidomide; MTX = methotrexate.
[a]The patient suffered from chronic GVHD after his first transplant, which deteriorated following his second transplant (22 months and 1 month, respectively).

Table 2 Clinical data of lesions treated and VAS scores per treatment session

Patient no.	*Treatment no.*	*Location*	*VAS before*	*VAS during*	*VAS after*
1	1	Labial mucosa and lips	10	0	10
	2	Labial mucosa	8	0	2
	3	Buccal mucosa, labial mucosa	8	2	0.5
	4	Labial mucosa	10	6	7
	5	Labial mucosa	10	1	2
2	1	Tongue	10	0	8
	2	Tongue	10	10	10
	3	Palate	8	7	6
	4	Palate	4	0	2
	5	Gingiva	9	8	6
	6	Tongue	8	0	5
	7	Buccal mucosa	6.5	4	2.5
	8	Gingiva	8	7	4
	9	Palate	8	7	5
3	1	Tongue	7	7	7
	2	Labial mucosa	5	0	1
4	1	Buccal mucosa	8	0	5
Average of 17 treatments			8.09	3.47	4.88

No. = number; VAS = visual analogue scale.

Table 3 Summary of VAS improvements per patient

Patient no.	*No. of treatments*	*Average VAS*		
		Before	*During*	*After*
1	5	9.2	1.8	4.3
2	9	7.9	4.8	5.4
3	2	6	3.5	4
4	1	8	0	5

No. = number; VAS = visual analogue scale.

was discontinued. The albumin levels remained in the normal range in the other patients (37 and 36 g/l).

Discussion

The CO_2 gas laser emits infrared radiation at a wavelength of 10.6 μm. At this wavelength, water absorption and, therefore, soft-tissue absorption is extremely high. The CO_2 laser is the most effective laser for soft-tissue incisions, excisions and vaporization. Thus, the CO_2 laser was accepted rapidly for surgical procedures.[12] In contrast to low-intensity lasers, to date, the analgesic effect of the CO_2 laser has been reported in one case series for the palliation of aphthae.[9] Our pilot study presents the success of CO_2 laser application for pain control in oral GVHD. In our study, an improvement in technique was extrapolated by the lack of requests for local anesthesia during treatment.

There is little data available on the two major aspects of the management of mucosal lesions with the CO_2 laser. (1) Healing of mucosal lesions has been reported by Loh *et al*.[13] In total, 10 patients with lichen planus were treated with a CO_2 laser at a power output of 5 W under local anesthesia. Although this paper concluded that the CO_2 laser contributed to the clinical improvement of the oral lichen planus, the recurrence rate during the 3-year follow-up period was unclear. In addition to removing the mucosal lichenoid lesion, Loh *et al* noticed a side effect of an immediate relief of the associated burning sensations and an increased tolerance to hot and spicy foods in all patients. This symptomatic improvement lasted throughout the follow-up period. (2) Pain relief using the CO_2 laser has been reported by Colvard *et al*.[9] In all, 18 patients with 25 separate minor RAU were treated. Their treatment protocol included pre-operative pain medication, local anesthesia, radiation of each lesion with 4 W of CO_2-generated photon energy and, if necessary, post-operative analgesics. During treatment with the laser, as much necrotic tissue as possible was removed. In all, 88.8% of patients in Colvard's study were completely pain free following anesthetic resolution, and none of the patients required post-operative medication for pain relief. The healing process was with minimal edema. Colvard *et al* were the first to recognize the potential use of the CO_2 laser in providing pain alleviation for RAU.

In our case series, a defocused beam of a CO_2 laser at minimal power (1 W) was used for mucosal pain relief. The lower laser emission output enabled treatment without local anesthesia. Pain relief was noted when analyzed both on a per treatment session basis and on a per patient basis. No effect on oral mucosal tissues, such as coagulation or vaporization, was visible. The treatment led to an improved nutritional status, indicated by the blood albumin levels and by the termination of total parenteral nutrition needs in one patient. Improved nutrition reflecting better oral functioning was noted following CO_2 laser treatment. This improvement was coincident with a decreased intake of systemic analgesics, emphasizing the local effects of the laser treatment.

Our ability to compare the responses per anatomical site is limited because of the small number of patients in the study. The overall impression from the VAS scores is of a favorable effect, with less improvement following treatment of the tongue.

Although our present study group was small and the follow-up period was limited, our findings have important implications with respect to sparing potential side effects of systemic analgesic medication. In patients with a high morbidity and mortality, such as in this group, any treatment added to the supportive repertoire is significant.

Most of the patients enrolled in this study were immunocompromised. The CO_2 laser allows control of the lesions with limited tissue penetration, thus minimizing damage to underlying tissues. Additional benefits of the laser include the presumed reduction of bacterial load and coagulation of bleeding areas.[14,15]

Caution must be exercised when using the CO_2 laser, and strict parameters were adhered to in the present study. High-power CO_2 laser can cause mucosal damage, in a manner similar to the classic effects of CO_2 lasers, namely incision, excision and vaporization of tissues. All these effects should be avoided when using the device for an analgesic effect.

The underlying mechanism of the analgesic effect of the CO_2 laser is as yet unknown. It was speculated to be the result of microcoagulation or sealing of nerve endings.[16] This theory contradicts a recent study showing that the number of intact peripheral nerve structures in laser-treated sites were similar to the numbers in cautery- and scalpel-treated sites.[17] Another possible explanation is based on the findings that the activation of peripheral inhibitory nerves decreases neural signals from the spine to the cortex (gate theory).[11] In contrast, Tran *et al*[10] documented a central somatosensory cortical effect of peripheral dermal stimulation with the CO_2 laser. These neural mechanisms are supported by the rapid improvement in sensory perception after the CO_2 laser treatment in our study. An interesting explanation for the analgesic effect of low-intensity diode laser, based on clinical[18] and laboratory[19] studies, showed an alteration in prostaglandin levels, consequently increasing the anti-inflammatory effect. However, the CO_2 laser–tissue interaction may not be the same as the low-intensity laser.

In this study, a new indication is suggested for a CO_2 laser in symptomatic treatment of mucosal lesions. The elevated analgesic response rate to a high-intensity laser, without local anesthesia, indicates a promising treatment modality. More research is warranted to confirm the analgesic effects of the CO_2 laser in large-scale studies to investigate the biologic mechanisms and significance of this analgesic effect and to determine the indications for laser therapy in oral medicine.

Acknowledgements

We would like to thank Dr Sharon DM Robinson for the editorial assistance. We would like to thank ESCq/Sharplan/Luxar group – Lumenis™ (OpusDent™) for facillitating the treatment with the Opus20™ device.

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