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Relieving Pain in Oral Lesions of Pemphigus Vulgaris Using the Non-ablative, Non-thermal, CO_2 Laser Therapy (NTCLT): Preliminary Results of a Novel Approach

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Abstract

Introduction: Pemphigus vulgaris (PV) is a chronic, serious autoimmune mucocutaneous bullous disease. Oral lesions in PV may be extremely painful. This pain may adversely affect the patients' oral intake and quality of life. This before-after clinical trial was designed to assess the pain relieving effects of single session of non-ablative, non-thermal CO_2 laser therapy (NTCLT) in oral lesions of PV.

Methods: Fifty painful oral lesions of fourteen patients with PV were illuminated by CO_2 laser (power: 1 W, scanning the lesions with rapid circular motion of the handpiece) passing through a thick layer of transparent gel with high water content. The pain severity of the oral lesions was reported by the patients up to the fourth postoperative day. They were also asked to continue their existing systemic treatment during the course of this study as a precondition for the participation.

Results: The severity of contact and non-stimulate (non-contact) pain declined immediately and significantly after NTCLT ($P<0.001$). The pain relieving effect was sustained during the four successive days of follow-up. The procedure was pain free and no kind of analgesics was required. Following NTCLT, there were no visible thermal complications such as destruction, ablation or irritation of the oral lesions.

Conclusion: The results of the trial proposed that single session of NTCLT could immediately and significantly relieve pain in oral lesions of PV, without any visible thermal complications.

Keywords: CO_2 laser; NTCLT; Pemphigus vulgaris; LLLT; Laser phototherapy.

Introduction

Pemphigus vulgaris (PV) is a chronic, rare but potentially life-threatening bullous disease of the mucous membranes and skin with established autoimmune nature. PV can affect all races, however the epidemiological studies report the highest prevalence of PV in people of Jewish ancestry and Mediterranean area. The prevalence of PV is 30/100 000 and annual incidence rate varies from 1 to 5 in 100 000 in different investigations carried out in Iran.[1,2] The most common presenting sign of PV are persistent painful mucosal erosions, especially of the oral cavity which may be the only/sole sign of the disease preceding the development of bullous skin lesions for weeks to months. The flaccid blisters in oral cavity are very fragile, rupture easily, leaving painful erosions. PV oral lesions may be extremely painful. The severe pain of these lesions

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can adversely affect the nutritional intake and quality of life of the patients.[3,4]

The mortality rate of PV has declined considerably after treatment with high doses of systemic corticosteroids in combination with adjuvant immunosuppressive drugs. Since PV is severe and life threatening, it is rational that the majority of investigations have focused on improving the therapeutic options for suppression and remission of the disease and rarely to the pain management of the oral lesions.[5] However, the considerable delay in remission of the oral lesions allows plenty of opportunities for complications such as malnutrition and dehydration to develop, due to the pain of the oral lesions.[5] In addition, the pain of the oral lesions may interfere with taking oral medications necessary for the control of the disease. Therefore, it seems necessary to obtain novel analgesic options for oral lesions of PV during conventional systemic treatment.

Low-level laser therapy (LLLT) or laser phototherapy is a fast-growing technology mainly applied clinically for pain relief, accelerating wound healing and anti-inflammatory effects for decades.[6]

For decades, CO_2 laser has served as a helpful surgical appliance for incision, excision, vaporization and coagulation. Recently, some investigators have reported the benefits of CO_2 laser application in a non-ablative, non-thermal manner as a low level (low intensity, phototherapeutic) laser for significant and immediate pain relief in some oral lesions with no thermal complications. In these studies, irradiation of painful oral lesions was performed through a layer of transparent high water containing gel with no analgesic properties in order to prevent thermal damage.

The painful oral lesions were illuminated through a layer of transparent gel with high water content in order to reduce the beam absorption by the lesion and prevention of tissue injury. The patients reported significant and immediate pain relief after laser treatment. The process was pain free with no need to anesthesia. No kind of thermal complications were observed after laser treatment.[7-11] This non-destructive technique was initially called non-ablative CO_2 laser therapy (NACLT) and non-thermal CO_2 laser therapy (NTCLT) afterwards. The results of thermometry and powermetery confirmed the low level phototherapeutic character of NTCLT.[9]

NTCLT has been used for immediate and significant pain relief in some painful oral lesions.[9,10,12,13] The study being reported in this paper was designed to evaluate the NTCLT pain relieving effects on PV oral lesions.

Methods

Study Design

This study was designed as a before-after open study. All of the referred patients were evaluated before inclusion in the study. Before taking the informed consent, the entire process used in the study and its investigational character were explained to all of the patients. The patients were well-advised that this procedure might have an impact only on the reduction of the pain caused by the lesions. They were also asked to continue their existing systemic treatment during the course of this study as a precondition for the participation.

Patient Selection

The inclusion criteria were: presence of pathognomonic H&E histologic findings and positive direct immunofluorescence (DIF) test for PV supporting clinical features, existence of painful oral pemphigus lesions interfering with eating, continuation of the systemic treatment for PV disease. Patients with age less than 18, photosensitivity and current pregnancy or lactation were excluded.

Study Procedure

Before laser irradiation, the lesion and its surrounding were covered with a thick (3-4 mm) layer of a transparent gel with high water (87.5%) content (Abzar Darman Co., Iran). The patient and surgical staff used appropriate protective eye glasses during the treatment.

The CO_2 laser (10600 nm; Lancet-2, Russia) was operated at 1 W power, in a continuous defocused mode, 5-6 mm distant from the surface of the gel while scanning rapidly over the lesion with a circular motion. In each pass, the laser energy was delivered to a circle area of the lesion (nearly1cm diameter) for 5 seconds and repeated immediately if the contact pain of the lesion persisted. The gel was gently wiped between the passes, and a new layer of gel was placed on the lesion to prevent from decreasing the water content of gel and tissue damage. The procedure was pain free and no kind of anesthesia was needed.

Assessments

The patients graded and recorded the contact and non-stimulate (non-contact) pain severity of their lesions before NTCLT, immediately after treatment and at 4, 8, 12, 24 hours post-operatively and then daily for up to 4 successive days. Patients were visited by the evaluator physician on daily basis in search for any kind of adverse effects.

Statistical Analysis

Data regarding the patients' responses were analyzed by SPSS version 13. The results were expressed as mean ± standard deviation (SD). Statistical significance was tested with Student's *t* test for paired samples and repeated measurement analysis. $P < 0.05$ was regarded as statistically significant.

Results

Fifty painful oral lesions of fourteen patients with PV recruited in the trial. The age range of patients was 33-86 years (mean, 47.7 ± 14.7 years). The means of the baseline visual analogue scale (VAS) pain scores for non-stimulated (non-contact) and contact pain of the lesions were 4 ± 1.6 and 7.5 ± 1.6 respectively. Immediately after NTCLT, the scores for non-stimulate (non contact) and contact pain decreased dramatically to zero in nearly all patients ($P < 0.001$), and continued until the end of

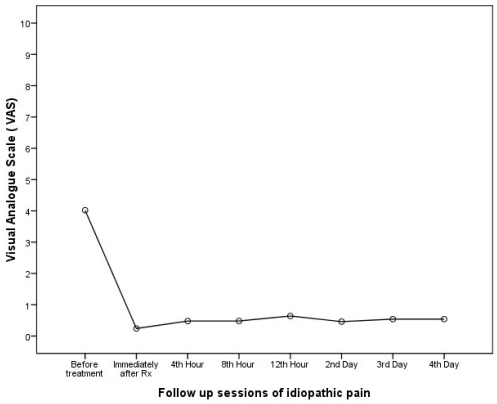

Figure 1. Mean Non-contact Pain Scores (VAS) in Follow up Sessions

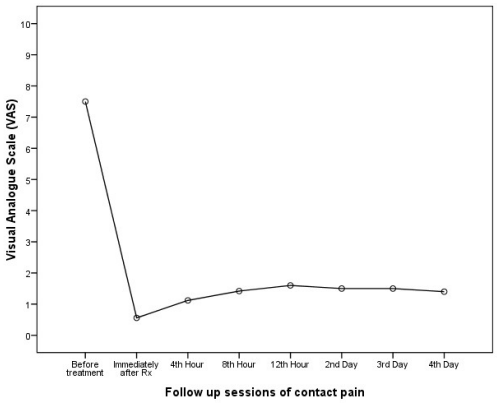

Figure 2. Mean Contact Pain Scores (VAS) in Follow up Sessions

the follow up periods with a mean range of 0.24 to 0.64 for non-stimulate pain score and 0.56 to 1.6 for contact pain score. (Figures 1 and 2) These differences between the mean scores of both non-stimulate and contact pain were also statistically significant throughout the follow up periods in comparison with the baseline pain scores ($P < 0.001$). The laser procedure was painless and no kind of anesthesia was needed. None of the patients reported warmth sensation in oral cavity during NTCLT. The evaluator physician recorded no visible thermal complications such as burn, destruction, ulceration or irritation of the lesions after NTCLT. At the end of the follow up sessions, the patients had no sensory loss in laser treated areas. There was no plume formation during NTCLT.

Discussion

This before-after clinical trial suggested that single session of NTCLT as a photobiomodulative procedure can be used in order to relieve pain immediately and dramatically in oral lesions of PV. The laser protocol was painless with no need to anesthesia. There was no aggravation of the lesions or visible thermal side effects following the application of NTCLT. To the best of authors' knowledge, this is the first study to report the pain relieving effects of non-thermal CO_2 laser application in oral lesions of PV.

LLLT (also known as "low intensity laser therapy, LILT," "low power laser therapy," "laser phototherapy," "soft laser therapy," "cold laser therapy," "photobiostimulation," "photobiomodulation," "non-ablative irradiation," etc) is a fast-growing technology used for pain relief, accelerating wound healing and anti-inflammatory effects.[6] Today, the applications of laser phototherapy have expanded to include serious diseases, e.g. myocardial infarction, stroke, traumatic and degenerative brain disorders diseases. Laser phototherapy is increasingly recognized as a valuable and safe option for pain management.

It should be noticed that in addition to the traditional low power phototherapeutic lasers (such as He-Ne laser, GaAs, GaAlAs and InGaAIP lasers) by some considerations, surgical lasers can also be used as low level lasers, for example; ruby laser 694 nm, CO2 laser 10 600 nm, and neodymium-doped yttrium aluminum garnet (Nd: YAG) laser 1064 nm all in defocused mode can be applied for laser phototherapy. As Tuner once said "When high power lasers are used for biomodulation, one only needs to make the beam wide enough not to burn. An alternative is to scan rapidly over the lesion with a narrow beam. Therefore, the power density or average power is kept low enough to avoid burning, and their incident energy and power density are set within the low intensity laser therapy range." The interesting experiment of Endre Mester with a low-powered ruby (694 nm) laser irradiation on the shaved areas of the back of the mice and faster regrowing of the hairs can be considered as the first demonstration of photobiostimulation by a surgical laser.[14,15]

With the purpose of application of the CO_2 laser as a low level, photobiomodulative laser for NTCLT, the CO_2 laser energy should be delivered not only by a de-focused hand piece moving in a circular manner in order to scan rapidly the whole surface of the lesion, but also through a thick layer of high water content, transparent gel capable of reducing the beam absorption by the tissue and prevent unwanted tissue burn or injury. By these considerations, the final laser power output after irradiation through the gel drops considerably by a factor of 200-500, and CO_2 laser can be used as a low level, phototherapeutic laser without any visible thermal side effects.[9]

Recently, investigators have demonstrated the benefits of CO_2 laser application in non- destructive manner for pain reduction of some oral lesions.[7-9,16] In order to evaluate the pain relieving effects of CO_2 laser beam in graft-versus-host-disease (GVHD), Elad et al kept the surface of the lesions wet during irradiation to prevent mucosal damage. They used CO_2 laser treatment for four patients with oral GVHD within 17 sessions.[7] The CO_2 laser (power: 1 W, 2-3 s/1 mm^2) was applied over mucosal lesions. Since the procedure was painless, anesthesia was not needed. The average VAS pain scores before, during, and immediately after treatment were 8.09, 3.47, and 4.88 respectively. There were not any visible complications following CO_2 laser irradiation.[7]

In another case report, oral aphthous ulcers of two patients were treated with CO_2 laser (power: 1.0-1.5 W, with a defocused hand piece for 5 seconds) through a thin film

of Elmex gel (a transparent gel with high water content). Immediately after laser irradiation, the patients reported pain relief without any visible complication. The procedure was free of pain and no kind of anesthesia was not needed.[8]

In another randomized control trial (RCT), the pain reliving effects of single session of non ablative, non thermal CO_2 laser irradiation was evaluated in minor recurrent aphthous stomatitis (miRAS) as a prototype of painful oral lesions.[9] In this RCT the investigators randomized 30 minor aphthous ulcers of 15 patients in to laser and placebo groups. Before laser therapy, a thick (3-4 mm) layer of high water content gel (87.5% water) with no anesthetic properties was placed on both the placebo and laser lesions. The laser group lesions were illuminated with CO_2 laser (power: 1 W, in de-focused continuous mode, scanning rapidly over the lesion for 5-10 seconds). This RCT demonstrated that immediately after single session of non-ablative CO_2 laser treatment, the pain of the lesions relieved significantly ($P < 0.001$), so that the patients in laser group could eat and drink easily immediately after treatment. This pain relieving effect was sustained during the four days follow-up periods. The procedure was not painful and no kind of anesthesia was required. After laser therapy, no visible thermal complications were observed such as burn, destruction, ulceration, or irritation of the lesions.[9]

Another pilot RCT demonstrated a favorable analgesic effect of NTCLT randomized 10 major aphthous ulcers of 5 patients into laser and placebo groups. The ulcers in laser group received the same laser protocol of Zand et al[10]; however according to the larger size of the major aphthous ulcers, more than one pass of NTCLT were applied. The results of this pilot study proposed that application of only one session of NTCLT could provide immediate and significant pain relief in major oral aphthous ulcers ($P < 0.001$) with no visible thermal complications so that the differentiation of pictures of before/after laser lesions was not easy.

Prasad and colleagues performed an RCT on 25 patients with 50 minor aphthous ulcers. In laser group, the lesions were illuminated through a layer of high water (90%) content gel with CO_2 laser (10600 nm, power: 0.7 W, continuous mode with a defocused hand piece for 5-8 seconds). This protocol provided immediate analgesic effect which sustained over 24 hours.[11]

After these primary evidences of analgesic properties of NTCLT in recurrent aphthous stomatitis, we decided to appraise the analgesic effects of single session of NTCLT in painful oral lesions of PV. Fourteen patients with 50 areas of PV, treated with conventional systemic treatment of the disease, were included in the study. The results of this before-after clinical trial proposed that application of single session of NTCLT could provide immediate and significant pain relief in oral lesions of PV ($P < 0.001$) with no visible thermal adverse effects or irritation of the lesions. The pain relieving effect continued during the four days follow-up periods. None of the patients reported warmth sensation in their oral cavity during NTCLT. The NTCLT procedure was painless and no anesthetic agent was needed. There was no tissue ablation or plume formation during the process, which increased the safety of the procedure for the surgeon and operating room staff.

In the review of literature, there were few reports on the application of other laser systems for pain reduction of PV oral lesions. In a case report, the investigators used LLLT as an adjuvant in two cases of PV. The patients had received systemic corticosteroid and dapsone. Their oral lesions were irradiated with diode laser (660 nm, 100 mW output power, 2 J per point, fluence: 35 J/cm^2 per point, time: 20 seconds per point). Immediately after the first session of LLLT, the patients reported approximately 70% oral pain reduction. Complete pain relief was reported after the third sessions.[17]

In another case report, Bhardwaj and colleagues reported the benefits of CO_2 laser application, as a classic surgical laser in two cases of painful recalcitrant oral PV.[18] The patients had received systemic corticosteroid and cyclophosphamide for 6-8 months. The painful lesions were irradiated at 1.0-1.5 W in a defocused manner for 5-10 seconds. They reported pain relief and improved wound healing after laser irradiation. In this study, the laser power used was low, however it was in the range of thermal, surgical lasers, and the lesions were ablated and coagulated. Certainly this procedure is quite different from NTCLT as a low intensity (photobiomodulative) laser procedure. It seems that the analgesic effects of surgical CO_2 laser in the study of Bhardwaj et al can be explained with the concurrent photobiomodulative effects of CO_2 surgery. The same concept that Kaplan et al stated in 1996.[19]

It should be noticed that some researchers who used the conventional, thermal effects of CO_2 laser in surgery (for cutting, ablation, destruction and coagulation of the lesions) reported less postoperative pain following CO_2 laser surgery.[19-22] Kaplan et al explained the lower postoperative pain experienced with CO_2 laser surgery to the concurrent low level laser phototherapeutic (photobiomodulative) effects of high power CO_2 laser surgery.[14,19,23] Kaplan et al stated that: *"Laser surgery and low level laser therapy should be regarded as two sides of the same coin."*[14,19,23] In fact, the analgesic effects of thermal CO_2 laser treatment in Bhardwaj study can be explained by the concurrent low power laser therapeutic (photobiomodulative) effects of CO_2 laser surgery.

Certainly, NTCLT as a non-thermal, low intensity (photobiomodulative) laser procedure is quite different from using surgical, thermal CO_2 laser irradiation in Bhardwaj study. As discussed above, following NTCLT, there were no visible adverse effects of thermal complications such as destruction, ulceration or even erythema.

Since PV is a serious and life threatening disease without appropriate systemic treatment, the patients should be informed that application of NTCLT cannot substitute the systemic therapy of the disease, as we instructed our patients to comply with their prescribed medical regimen.

In order to clarify the mechanisms of the pain relieving

effects of NTCLT, powermetery and thermometery were performed in our previous studies.[9] These studies confirmed the low power, non-thermal nature of applied CO_2 laser in this laser procedure. This technique was initially called NACLT, however after demonstrating the non-thermal nature of the technique, it was called NTCLT to avoid misinterpretation with high power fractional non- ablative CO_2 lasers used for skin rejuvenation. In fact, NTCLT as a non-thermal, low intensity (biomodulative) laser protocol is not only quite different from conventional high power CO_2 lasers irradiation, but also should not be misinterpreted with fractional non-ablative CO_2 lasers, which are high power, thermal lasers too.

Since the pain relieving effect of NTCLT is immediate, we suppose that physiological neural changes such as blockage of action potential generation and slowing the conduction velocity of nociceptive signals in small diameter, unmyelinated C and thinly myelinated A δ fibers might participate in this pain relieving effect. Morphological changes of the nerve endings especially reversible varicosity formation might be another hypothesis in this field. Nerve endings destruction is less likely to be provoked by NTCLT, because, even the investigators who applied CO_2 laser as a classical surgical instrument, reported no statistically significant difference between the number of intact peripheral nerves of laser-treated sites and sites treated with scalpel or electro cautery.[24] We do not know whether the other presumed mechanisms, such as increase in β-endorphin synthesis and release,[25,26] blockage of acetylcholine,[26] reduction of bradykinin and prostaglandins synthesis,[27] suppression of Substance P,[28] changes in nitric oxide[29] and other chemicals- proposed to play at least a part in pain relief of low level phototherapeutic lasers- participate in analgesic effect of NTCLT, or not. Further basic studies are needed to clarify the real mechanisms of this analgesic effect.

This pilot study had some limitations. The low incidence of PV did not allow a control group to be included in the study, so the potential placebo effect of the procedure could not be could not be excluded completely. In this pilot study, the pain of the patients was followed up for four days. We recommend that further studies (if possible as RCTs) consider larger sample sizes and extending the follow-up periods. In addition we recommend that in further studies the pain relieving effects of NTCLT and conventional low power lasers (such as diode lasers) be compared with each other in oral lesions of PV.

Although in this trial we used eye glasses matched to the CO_2 laser wavelength (10 600 nm), we highly recommend the application of eye glasses matched to both the 10 600 nm and the guiding beam for eye protection against the reflected beam from the gel surface

In conclusion, the results of this trial proposed that NTCLT can be potentially considered as a novel alternative option for pain relief in oral lesions of PV. However the patients should continue their conventional treatment of PV, and understand that this pain relieving procedure cannot substitute the systemic treatment of the disease. This laser-based technique can improve both the patient's oral intake (food and medication), and their quality of life, the concepts which should be evaluated in further studies.

Ethical Considerations

The study protocol received approval from the Clinical Ethics Committee of Tehran University of Medical Sciences, branch of the Academic Center for Education, Culture and Research (ACECR).

Conflict of Interests

The author has no conflict of interest to declare.

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