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Pulsed versus continuous wave low-level light therapy on osteoarticular signs and symptoms in limited scleroderma (CREST syndrome): a case report

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Abstract. Limited cutaneous systemic sclerosis (lcSSc) was formerly known as CREST syndrome in reference to the associated clinical features: calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias. The transforming growth factor beta has been identified as a major player in the pathogenic process, where low-level light therapy (LLLT) has been shown to modulate this cytokine superfamily. This case study was conducted to assess the efficacy of 940 nm using millisecond pulsing and continuous wave (CW) modes on osteoarticular signs and symptoms associated with lcSSc. The patient was treated two to three times a week for 13 weeks using a sequential pulsing mode on one elbow and a CW mode on the other. Efficacy assessments included inflammation, symptoms, pain, health scales, patient satisfaction, clinical global impression, and adverse effects monitoring. Considerable functional and morphologic improvements were observed after LLLT, with the best results seen with the pulsing mode. No adverse effects were noted. Pulsed LLLT represents a treatment alternative for osteoarticular signs and symptoms in limited scleroderma (CREST syndrome). © 2014 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JBO.19.11.118001]

Keywords: limited cutaneous systemic sclerosis; low-level light therapy; CREST syndrome; transforming growth factor beta; pulse structure; continuous wave mode; photobiomodulation; osteoarticular symptoms and signs.

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1 Introduction

Scleroderma, or systemic sclerosis (SSc), is a lifelong condition characterized by vasculopathy, fibrosis of skin and various internal organs, and inflammation or autoimmunity.^{1,2} Systemic scleroderma is a rare disorder, with an annual incidence in the United States of about 20 cases per 1 million adults, and a prevalence of 100 to 300 per 1 million population.^{3,4} It is more common among women than men, and in certain groups such as Native Americans.^{3,4}

Limited cutaneous SSc (lcSSc) is part of the heterogeneous group of sclerodermas. LcSSc was formerly known as CREST syndrome in reference to the associated clinical features: calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias. This connective tissue disease typically has gradual onset and disease expressions are restricted to certain areas of the skin.⁵ In patients with lcSSc, the core manifestations of the disease, including skin calcifications, are mostly confined to the fingers, hands, and forearms distal to the elbows, with or without tightening of the skin of the lower extremities distal to the knees. Cutaneous telangiectasias on the face are also seen, along with varying degrees of internal organ involvement. Proximal extremities and the trunk are not involved. LcSSc may be debilitating and influences a person's ability to participate in activities of daily life in different ways.⁶⁻⁸

Although the pathogenesis of this condition is unclear, a number of studies have suggested that the transforming growth factor beta (TGF- β) is an important candidate in the pathogenic process.⁹⁻¹² TGF- β is a prototypic profibrotic cytokine that

increases collagen synthesis by fibroblasts and downregulates extracellular matrix degradation. Evidence comes from past studies reporting, for instance, a TGF- β upregulation, an increase in the expression of TGF- β receptors, as well as the observation that the blockade of endogenous TGF- β signaling prevents upregulated collagen synthesis in scleroderma fibroblasts.¹³⁻¹⁵ TGF- β is also known to be involved in immunomodulatory activities. Thus, TGF- β appears to be a sound target for therapeutic intervention.^{16,17}

Interestingly, low-level light therapy (LLLT) with red to near-infrared (NIR) wavelengths has been shown to trigger natural intracellular photobiochemical reactions including TGF- β modulation.¹⁸⁻²¹ Red to NIR light is thought to be absorbed by mitochondrial respiratory chain components.^{22,23} Absorbed light converted to chemical kinetic energy results in the increase of reactive oxygen species and adenosine triphosphate, initiating a signaling cascade which can modulate the expression of growth factors and cytokines.²⁴⁻²⁷ Hence, LLLT might be helpful in the treatment of symptoms associated with lcSSc.

This case study was conducted to assess the efficacy of NIR (940 nm) LLLT using millisecond (ms) pulsing and CW on osteoarticular signs and symptoms associated with lcSSc.

2 Materials and Methods

2.1 Case Description

The patient was a Caucasian 34-year-old female with Fitzpatrick phototype II. She had a 13-year history of symptoms and presented with the following features of the disease: generalized

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calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectasia. There was no history of esophageal dysmotility. The extent of her calcinosis affected her forearms, chin, face, and buttocks. She underwent a surgical procedure to remove calcifications from her buttocks. The patient presented with elbow mobility restrictions. She had a history of juvenile dermatomyositis (quiescent). Her medication included Coumadin and Adalat. She failed to respond to a variety of pharmacological treatments including methotrexate. The patient was initially referred to our clinic by her rheumatologist in December 2010.

She initially received a series of LLLT treatments (940 nm) three times a week on her face and chin over a 6-month period, using Lumiphase technology (OPUSMED Inc., Montreal, Canada).

2.2 Study Procedures

This was a single-blind within subject case study, where the left forearm was randomly assigned to receive LLLT using sequential pulsing mode and the right forearm assigned to LLLT using a CW mode.

The patient was treated two to three times a weeks for 13 weeks with 940 nm, using LumiPhase™ technology (OPUSMED Inc.). For the sequential pulsing mode, the power density was of 60 mW/cm² for a total fluence of 81 J/cm² (30 min). The pulsing patterns and time on-and-time-off sequences were as follows (see Fig. 1): Pulse duration (time on) 500 μ s, pulse interval (time off) 150 μ s, 4 pulses per pulse train, and a pulse train interval of 1550 μ s. For the CW mode, an irradiance of 60 mW/cm² was used for a total fluence of 81 J/cm² (15 min). The size of the treatment areas were 20 cm \times 10 cm, and the treatment distance was 4 ± 0.4 cm.

2.2.1 Digital photographs

Photographs (Canon Dual Flash EOS 10D, Canon, Tokyo, Japan with EX SIGMA 50 mm 1:2.8 macrolens, Sigma, Aizu, Japan) were taken before and at the follow-up visit. Each photograph was taken maintaining as much as possible the identical ambient lighting, pose, and camera angles.

2.2.2 Skin temperature monitoring

NIR radiation typically induces molecular vibrations and rotations and by so doing increases skin temperature.¹ Papillary dermis temperature was monitored at a depth of 1 and 3 mm with needle probes placed on the interior face of the left forearm

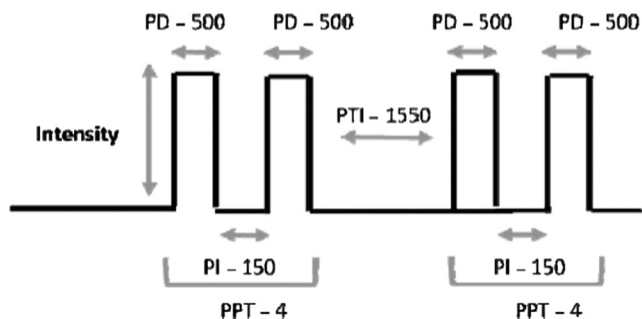


Fig. 1 Schematization of the sequential pulsing mode used on the left forearm. Pulse duration [time on (PD)] 500 μ s, pulse interval [time off (PI)] 150 μ s, 4 pulses per pulse train (PPT), and a pulse train interval (PTI) of 1550 μ s.

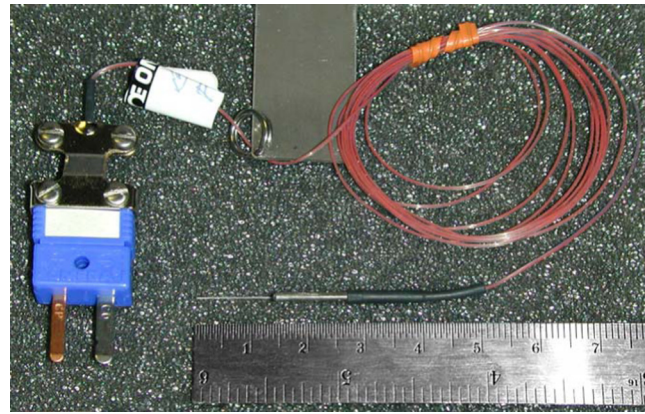


Fig. 2 Hypodermic needle probe inserted at 1- and 3-mm depth in the dermis during LLLT treatments.

throughout the LLLT session (Type-T thermocouple, Omega, Montreal, Canada; Fig. 2).

2.3 Patient Assessments

Efficacy assessments included the examination of inflammation, pain, and other signs and symptoms associated with the patient's condition, a clinical evaluation, and a patient satisfaction questionnaire. Treatment safety was examined by adverse effects monitoring. Assessments were conducted at baseline and after 13 weeks of treatment (endpoint). The clinical rater and the patient were blinded to which forearm received the pulsed or CW LLLT treatment.

2.3.1 Symptoms scale

For each forearm, the degree of morning stiffness, flexibility, elbow amplitude (flexion/extension), strength, ability to lift heavy objects (10 lb and more), mobility (rotation), calcium deposits (visually), ulceration, and skin thickness were rated. The percent improvement from baseline was recorded at endpoint.

2.3.2 Inflammation scale

The degree of swelling, tenderness, or warmth was rated using a 3-point scale (0 = none, 1 = moderate, 2 = severe) at endpoint.

2.3.3 Clinical assessment

The clinical global impression of change was rated at endpoint using a range of responses from 0 = none; 1 = mild; 2 = moderate; 3 = good; 4 = excellent.

2.3.4 Patient satisfaction

A series of 12 questions were asked to evaluate the extent to which the treatments received on each forearm met the patients' needs and expectations. Aside from yes/no questions, these were rated on a scale 1 to 7 (1 = worse outcome to 7 = best outcome). The list of questions is presented in Table 1.

2.3.5 Treatment-related adverse effects

The presence of discomfort, erythema, edema, and pain associated with the treatment was recorded.

Table 1 Patient satisfaction questionnaire.

Question	Pulse-Treated side	CW-Treated side
1. How satisfied or dissatisfied are you with the way the treatment relieved your symptoms?	7	5
2. How satisfied or dissatisfied are you with the ability of the treatment to prevent worsening of your condition?	7	7
3. How satisfied or dissatisfied are you with the amount of time it took for the treatment to start working?	7	7
4. How convenient or inconvenient was the amount of time necessary to administer the treatment?	3	5
5. Did you have any side-effects from the treatment?	No	No
6. How bothersome were the side effects of the treatment?	N/A	N/A
7. To what extent did the side effects interfere with your physical health and ability to function (i.e., pain)?	N/A	N/A
8. To what degree do the side effects affect your overall satisfaction with the treatment?	N/A	N/A
9. Overall, how confident are you that using this treatment was a good thing for you?	7	7
10. How certain are you that the good things about the treatment outweigh the bad things?	7	7
11. Taking all things into account, how satisfied or dissatisfied are you with this treatment?	7	7

3 Results

Figure 3 depicts the photographs of the patient's forearms at baseline and after 13 weeks of LLLT treatment using pulsed or CW delivery mode. Efficacy assessments revealed that both forearms improved after LLLT treatment. However, some differences, mostly in favor of the pulse-treated side, were seen in clinical outcomes.

The percent improvement from baseline was recorded at endpoint for symptoms associated with the patient's condition. As can be appreciated in Fig. 4, the degree of improvement was greater for most symptoms on the pulse-treated side in comparison to the CW-treated side, with the greatest difference seen for calcium deposits (40% for the pulse side versus 4% for the CW side). A small improvement (5%) was seen in favor of the CW-treated area for strength/ability to lift heavy objects. No difference between treatment sides was observed for ulceration and skin thickness. Symptoms assessment also revealed that only moderate tenderness was noted on both forearms, as documented on the inflammation scale conducted at the end of the treatment period; no swelling or warmth was observed.

The clinical assessment was rated at endpoint using a range of responses from 0 (none) through 4 (excellent). The CW-treated forearm was rated as moderately improved, whereas the change seen on the pulse-treated side was deemed excellent. The pattern of results was similar from the patient's perspective. At the end of the study period, the patient reported being very satisfied with various aspects of both treatments including the ability of the treatment to prevent worsening of symptoms and with the amount of time it took for the treatment to start working; the degree of satisfaction with symptom relief was, however, deemed superior on the pulse-treated side (Q.1 to Q.3). The amount of time necessary to administer the treatment was judged to be somewhat more convenient for the CW-treated forearm in comparison with the pulse-treated forearm (Q.4). The patient also reported no side effects from treatment (Q.5 to Q.8) on either forearm. The patient also judged that the treatment on both forearms was satisfactory outweighing the

downside and was overall very satisfied with the treatment (Q.9 to Q.10). The patient stated that she would recommend this treatment to other patients with a similar condition (Q.12). Responses for each forearm on the satisfaction questionnaire are presented in Table 1.

Both the pulse and CW LLLTs were well tolerated. Other than slight erythema noted on the left forearm, no significant



Fig. 3 Patient forearms before (upper panel) and after (lower panel) LLLT treatments. The left forearm receives LLLT using a sequential pulsing mode and the right forearm receives LLLT using a CW mode.

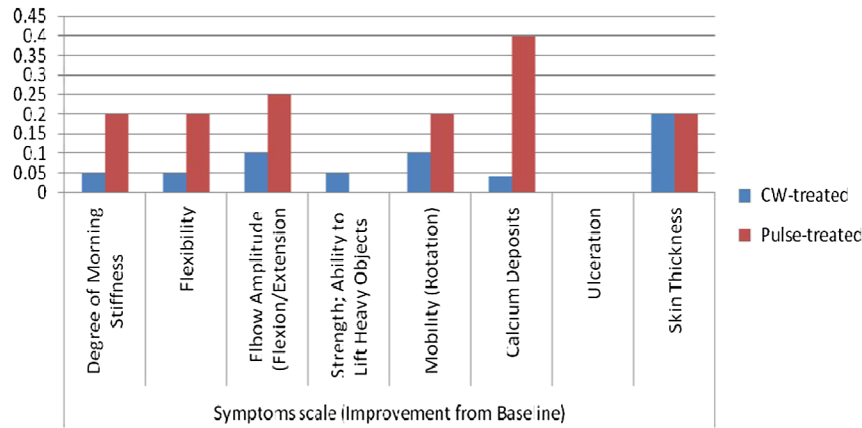


Fig. 4 Percent improvement from baseline at endpoint in the degree of symptoms for each forearm.

treatment-related adverse effects were noted during the entire study period including the presence of discomfort, edema, and pain.

In the present study, skin temperature was monitored. Temperature variations were registered by thermocouple hypodermic probes rigorously placed with adhesive tape and were never greater than 39.8°C at a depth of 1 mm and 38.3°C at 3 mm (typical treatment session temperature curves shown in Fig. 5). Monitoring attested that the skin temperature during LLLT application increased without reaching the skin injury threshold level (>42°C).

4 Discussion

Results from this case study suggest that 940-nm LLLT was efficacious in alleviating signs and symptoms associated with leSSc. Data from the clinical assessment revealed that the

LLLT significantly improved the appearance and severity of lesions. Benefits to the patient were also noted from the patient’s perspective. Furthermore, no treatment-emergent adverse effects were observed. Overall, significant functional and morphologic improvements following LLLT treatment were observed with the best results seen with the pulsing mode. One perceived advantage of the CW over the pulse delivery was the treatment duration; however, given the added benefits of the pulsed mode, this does not appear to be a significant drawback.

LLLT therapy appears to bring relief to patients affected by this debilitating disorder in a noninvasive manner. LLLT therapy potentially has two mechanisms of action: thermal and nonthermal. NIR wavelengths can raise skin temperature to 45°C—although the thermal effects do not create tissue injury—so as to provide inside-out heating possibly vasodilating capillaries which in turn increases catabolic processes leading to a

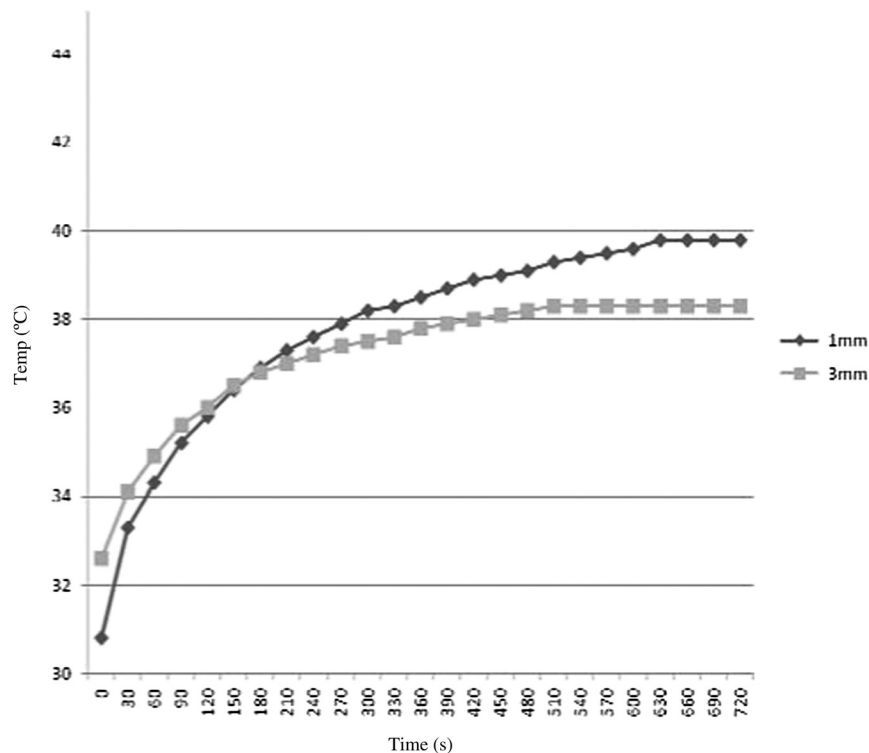


Fig. 5 Papillary dermis temperature monitoring with 1- and 3-mm needle probes throughout the LLLT session.

reduction of *in situ* calcinosis.²⁸ Second, nonthermal effects also take place presumably resulting in a cascade of cellular reactions including the modulation of growth factors and inflammatory mediators. It has been suggested that the LLLT anti-inflammatory effects are mediated via the activation of the TGF- β complex.^{18,19} In this mechanism, LLLT-emitted photons must be absorbed by a molecular chromophore. A growing body of evidence suggests that the photobiomodulation mechanisms are ascribed to the activation of mitochondrial cytochrome c oxidase.²⁹ Respiration in the mitochondria can be inhibited by nitric oxide (NO) binding to cytochrome c oxidase which competitively displaces oxygen and affects cell metabolism. Excess NO binding is associated with inflammatory processes, cell damage, and apoptosis. Light absorption dissociates NO, allowing cellular respiration to resume and normalization of cell activity, ultimately triggering biomolecular processes. Pulsed light delivery, as opposed to a CW mode, might favorably enhance this cellular strategy. Short and intermittent light emissions might enhance NO dissociation, therefore augmenting mitochondrial energy production and cellular activity.

Overall, these preliminary results suggest a beneficial effect on the alleviation and progression of symptoms. While these findings are encouraging, additional research in larger samples of patients is needed to further evaluate this promising therapy. Future studies should include long-term assessments to document maintenance of benefits over time. Further trials are also necessary to identify the cellular processes underlying the mechanisms at play in the therapeutic effect. In the future, LLLT may well become a new treatment option to provide enhanced daily relief to patients with this incapacitating condition. This novel therapeutic modality may broaden the currently restricted therapeutic armamentarium of the disease.

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