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Case Report

Prophylactic Low-Level Light Therapy for the Treatment of Hypertrophic Scars and Keloids: A Case Series

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Background and Objectives: Hypertrophic and keloid scars result from alterations in the wound healing process. Treating abnormal scars remains an important challenge. The aim of this case series was to investigate the effectiveness of near infrared (NIR) light emitting diode (LED) treatment as a prophylactic method to alter the wound healing process in order to avoid or attenuate the formation of hypertrophic scars or keloids.
Study Design/Patients and Methods: Three patients (age 27–57) of phototypes I–III with hypertrophic scars or keloids due to acne or surgery participated in this case series. Following scar revision by surgery or CO_2 laser ablation on bilateral areas, one scar was treated daily by the patient at home with non-thermal, non-ablative NIR LED (805 nm at 30 mW/cm^2) for 30 days. Efficacy assessments, conducted up to a year post-treatment, included the Vancouver Scar scale (VSS), clinical global assessment of digital photographs, and quantitative profilometry analysis using PRIMOS. Safety was documented by adverse effects monitoring.
Results: Significant improvements on the NIR-treated versus the control scar were seen in all efficacy measures. No significant treatment-related adverse effects were reported.
Conclusion: Possible mechanisms involved are inhibition of TGF-βI expression. Further studies in larger group of patients are needed to evaluate this promising technique. Lasers Surg. Med. 42:597–601, 2010.

Key words: CO_2 laser ablation; near infrared (NIR); photobiomodulation; prevention; surgical scars; transforming growth factor beta-I

INTRODUCTION

Wound healing is a complex tissue-response to injury leading to skin restoration. Alterations in the wound healing process can result in hypertrophic or keloid scarring. Cutaneous aberrant scaring, characterized by an imbalance between cell growth and excessive extracellular matrix deposition, can form after surgery, laser treatment or acne. Keloids take the form of a raised distorted growth that grow beyond the boundaries of the original wound site and are frequently associated with pruritus and pain. Hypertrophic scars have the clinical appearance of a red raised lump on the skin, do not extend beyond the original skin trauma area, and often regress with time to a certain extent. Aside from their appearance, clinical features and histological characteristics also distinguish between hypertrophic scars and keloids [1]. Recent research has underlined a lowered self-esteem and impaired quality of life in affected individuals which underlines the need for better treatment options for these patients [2]. Treating abnormal scars remains an important challenge for both the clinician and the affected person.

A wide range of surgical (e.g., cryotherapy, excision), non-surgical (e.g., pharmacological, mechanical pressure, silicone gel dressings), and laser therapies (CO_2, pulsed dye, fractional ablative, and non-ablative lasers) have been tested with variable success [1,3,4]. The inconsistencies and sub-optimal results obtained to date call for the investigation of new therapeutic interventions. Moreover, potential differential effects on keloids and hypertrophic scars must be considered in the search for new treatments [5].

Wound healing is a complex cascade of multistep physiologic events regulated at the biochemical level by a vast array of signaling mechanisms. Understanding the molecular mechanisms involved in the dysregulation of wound healing leading to aberrant scaring might allow the development of targeted therapies for keloids and hypertrophic cells. Recent evidence point to the transforming growth factor beta-I (TGF-βI) has a major player in the formation of hypertrophic scars and keloids [6–8]. Results of wound healing research over the past decades have demonstrated that keloidal and hypertrophic scar tissues show higher expression levels of receptors, overproduction

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and poor regulation of TGF-βI, leading to fibroblastic proliferation and excess collagen deposition. Thus, TGF-βI appears to be a promising target for therapeutic intervention.

It has been shown that low-level light therapy (LLLT) can trigger natural intracellular photobiochemical reactions involved in wound healing, including TGF-βI modulation [9–11]. LLLT with red light and near infrared (NIR) light acts on the mitochondria and at the cell membrane level [12]. Absorbed light converted to chemical kinetic energy causes changes in membrane permeability, improves signaling between mitochondria, nucleus and cytosol, nitric oxide formation and increase oxidative metabolism to produce more ATP, ultimately leading to normalization of cell activity [13–16]. Hence, LLLT might be helpful in scar treatment. The aim of this case series was to investigate the efficacy of LLLT, by means of light emitting diode (LED), as an adjunct prophylactic therapy to conventional scar revision interventions in the healing process of abnormal scars.

In the present case series, patients with bilateral abnormal scars were treated with LED in the NIR spectrum (805 nm, 30 mW/cm^2) following scar revision by surgery or CO_2 laser ablation on both sides. Patients self treated at home and daily for 30 days on one side of the affected area while the other side served as control, not receiving LED treatment (split-study; the patient being its own control). Clinical improvements were assessed with in vivo 3D microtopography quantitative measurement for scar height, blinded clinical assessment of change using digital photographs, and the Vancouver Scar scale (VSS). Cutaneous adverse response was also documented. It was expected that the NIR-treated side would yield better clinical outcomes in comparison to the control side.

STUDY DESIGN/PATIENTS AND METHODS

Case 1

The patient was a Caucasian 57-year old female with Fitzpatrick phototype II. The patient underwent face-lift surgery for treatment of facial chalasia (rhytides and laxity). The patient had no history of abnormal scarring. She was not taking any medication prior to and after surgery. Post-operative care consisted of standard wound care. The post-operative course was unremarkable until day 20 when abnormal wound healing was noted on pre-auricular areas bilaterally. Wound care then included massage and silicon sheets. On post-operative day 45, the diagnosis was confirmed (keloids) and the patient was referred to our clinic. Scar revision for this patient consisted in surgical removal of the scars with primary closure (see Fig. 1; upper panels; 1 week post-revision). Scar revision was performed 8 months after the facelift.

Case 2

The patient was a 27-year-old Caucasian male with Fitzpatrick skin type I. The patient presented with hypertrophic scars due to abnormal wound healing post-acne lesions of the chest (sternal area). The scars were 6-year old.

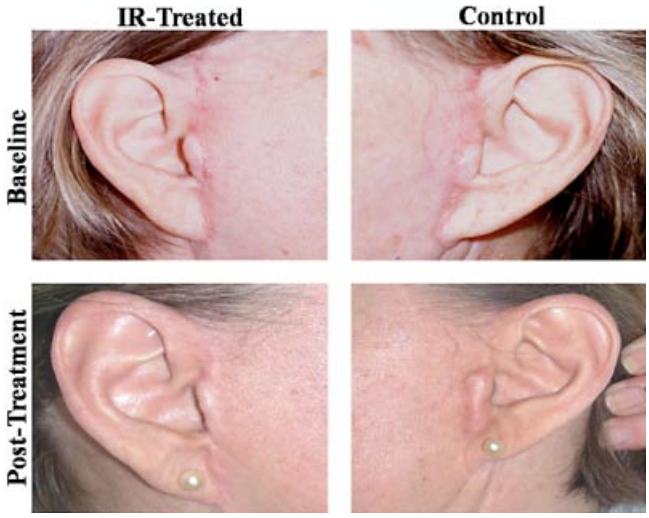

Fig. 1. Case 1 after pre-auricular scar revision (**upper panel**) and 1-year follow-up (**lower panel**). Left: NIR-treated side; Right: control side. [Figure can be viewed in color online via www.interscience.wiley.com.]

His past medical history was negative. He did not receive any medical treatment but used a topical cream with vitamin E. CO_2 laser ablation was performed to remove scar tissue. First, local anesthesia was completed with Xylocaine 2% with epinephrine 1:100,000. Then, the CO_2 laser was used in the focused bistouri mode (1 mm spot size, 15 W, CW mode) for debulking the scar in order to reduce the volume of the fibrotic lesion. What was left at the base of the lesion was further treated but in the resurfacing mode using a scanner to remove very thin layers of scar tissue. The CO_2 laser parameters were the following; 18 W, 7.1 mm dia, circles, 0.1 second on/0.1 second off, with up to five consecutive passes performed until normal skin was reached. Bilateral lesions (similar ones on each side) were chosen and treated the same way. Post-treatment wound care included daily application of topical antibiotics and a telfa dressing for 10 days.

Case 3

This patient was a 36-year old Caucasian female with Fitzpatrick phototype III presenting several bilateral hypertrophic scars as a result of surgical removal of nevi (areola area). The scars were 3-year old. She had experienced abnormal wound healing in the past with residual textural changes after trauma. Hypertrophic scars were raised by 2–5 mm and showed diffuse telangiectasia. No pain was present with occasional pruritus. CO_2 laser resurfacing was performed as described for Case 2.

Table 1 presents a summary of the patients characteristics.

Study Procedure

Following scar revision, one side was randomly selected (flip of a coin) for NIR treatment by the patient at home and daily for 15 minutes with LED emitting at 805 nm

TABLE 1. Patient Characteristics

ID	Case 1	Case 2	Case 3
Gender	F	M	F
Age	57	27	36
Phototype	II	I	III
Scar type	Pre-auricular linear keloids bilaterally	Hypertrophic scars on chest bilaterally	Hypertrophic scars on back bilaterally
Scaring cause	Post-face lift	Post-acne	Post-excision
Scar revision method	Surgical scar revision/excision	CO_2 laser resurfacing	CO_2 laser resurfacing
Scar age	8 months	6 years	3 years
Last assessment visit	Week 77	Week 12	Week 8

($30\,mW/cm^2$) at a treatment distance of 2.5 cm, for 30 days (total dose = $27\,J/cm^2$). Patients were instructed to start the NIR treatment upon their return home. Before returning home, patients received post-treatment wound care instructions, which included applying a topical antibiotics and a daily telfa dressing for 10 days. Furthermore, following the acute healing phase, sun avoidance and the use of a sunscreen (SPF 30) was mandatory in the unlikely event of direct sun exposure on the treated area. Digital photographs of the NIR-treated and control scars (Canon Dual Flash EOS 10D, Canon, Tokyo, Japan with EX SIGMA 50 mm 1:2.8 macro lens; Sigma, Aizu, Japan) were taken at base line and at follow-up visits. Each photograph was taken maintaining identical ambient lighting, pose, and camera angles.

Clinical Global Impression of Change (CGIC)

The photographs were analyzed for clinical improvement by a blinded non-treating physician using a 5-point scale for degree of improvement from baseline for NIR-treated and control scars (0 = none; 1 = mild; 2 = moderate; 3 = good; 4 = excellent).

Severity Assessment

A scar severity score was determined using the VSS for the NIR-treated and control scars by a blinded non-treating physician [17]. The Vancouver scale consists of four variables: vascularity, height (thickness), pliability, and pigmentation. Each variable has 4–6 possible scores. A total score ranges from 0 to 14, whereby a score of 0 reflects normal skin.

Skin Surface Topography

The measurements of the skin surface topography were performed using the Phaseshift Rapid in vivo Measurement of Skin optical 3D device (PRIMOS^{TM}, GFM, Teltow, Germany) on the NIR-treated and control areas to quantify scar height (Cases 2 and 3). To accurately assess the degree of improvement, scars were analyzed to determine the cross-sectional area after the pre- and post-topographical images were aligned. A cross-sectional line graph across each scar compared 24 points to determine the mean change from baseline to post-treatment. Related Samples Wilcoxon's signed rank test was used to assess the difference between pre- and post-scar heights.

Cutaneous Response

On each visit, the presence of adverse effects including erythema, edema, pruritus, hypopigmentation, hyperpigmentation, and textural changes were documented.

RESULTS

The CGIC assessment revealed a greater improvement on the NIR-treated scars in comparison to the control scars in the three patients (Table 2): clinical improvements were deemed "moderate" to "excellent" (scores 2–4) on the NIR-treated scars while the control scars yielded lesser degrees of improvements (score of 1 or mild). Clinical improvements in appearance and outline of the scars and can be noted for Case 1 in Fig. 1. Similarly, the VSS revealed a greater reduction in severity score on the NIR-treated scars in all cases in comparison to the control scars at follow-up. The greatest reduction in VSS for the NIR-treated scars was of 77% (Case 1) whereas for the control scars, of 29% (Case 2; Table 3). The measurements of the skin surface microtopography revealed that scar height was significantly reduced for the NIR-treated scars (Case 2: $P = 0.07$; Case 3: $P < 0.001$) but not for the control scars (Case 2: $P = 0.55$; Case 3: $P = 0.31$). Fig. 2 depicts digital photographs and surface microtopography analyses for the NIR-treated and control scars at baseline and post-treatment for Case 2.

Treatment was overall well tolerated with patients reporting a slight but bearable sensation of heat during the procedure. Aside from slight erythema and mild crusting following CO_2, no other adverse signs, such as post-inflammatory hyperpigmentation (PIH), were observed in patients.

TABLE 2. Clinical Global Impression of Change Individual Results

	NIR-treated	Control
Case 1	4	1
Case 2	3	1
Case 3	2	1

TABLE 3. Vancouver Scar Scale Individual Results

	NIR-treated			Control		
	Pre	Post	% Reduction	Pre	Post	% Reduction
Case 1	9	2	77.78	9	8	11.11
Case 2	11	7	36.36	7	5	28.57
Case 3	8	7	12.50	6	6	0.00

DISCUSSION

Keloids and hypertrophic scars are benign skin tumours and are the effect of a dysregulated wound-healing process. These scar types are difficult to eradicate and conventional treatments are not always successful. In the present study, we investigated the effect of LLLT by LED therapy in the reduction of aberrant scars following scar revision by CO_2 or surgery. Patients were treated in a within-subject design with NIR (805 nm) on one area while the other area served as control.

The results from this case series revealed that abnormal wound healing can potentially be modulated with LLLT and that the volume of scar tissue, reduced after surgical scar revision or CO_2 laser resurfacing in prone patients. The results from this case series also showed that LED therapy was well tolerated with no significant adverse reactions, likely due to the low-level characteristics of this treatment modality. Other light sources, such as PDL, often induce, although transiently, important adverse effects such as severe swelling, purpura, and erythema which may compel subjects to discontinue treatment. From a clinical perspective, the absence of thermal injury (peak power effects) to the skin during light treatment may yield a significant advantage over laser-based methods, given that improvements can be achieved without thermal damage and with limited adverse reactions.

NIR irradiation may enhance the wound healing process presumably by its biomodulatory effects. The mechanisms at play have not been investigated in the present context. It is possible that multiple cell signaling pathways contributed to the observed therapeutic effect. TGF-βI and other families of molecules have been shown to be modulated by LLLT, including transforming growth factor platelet-

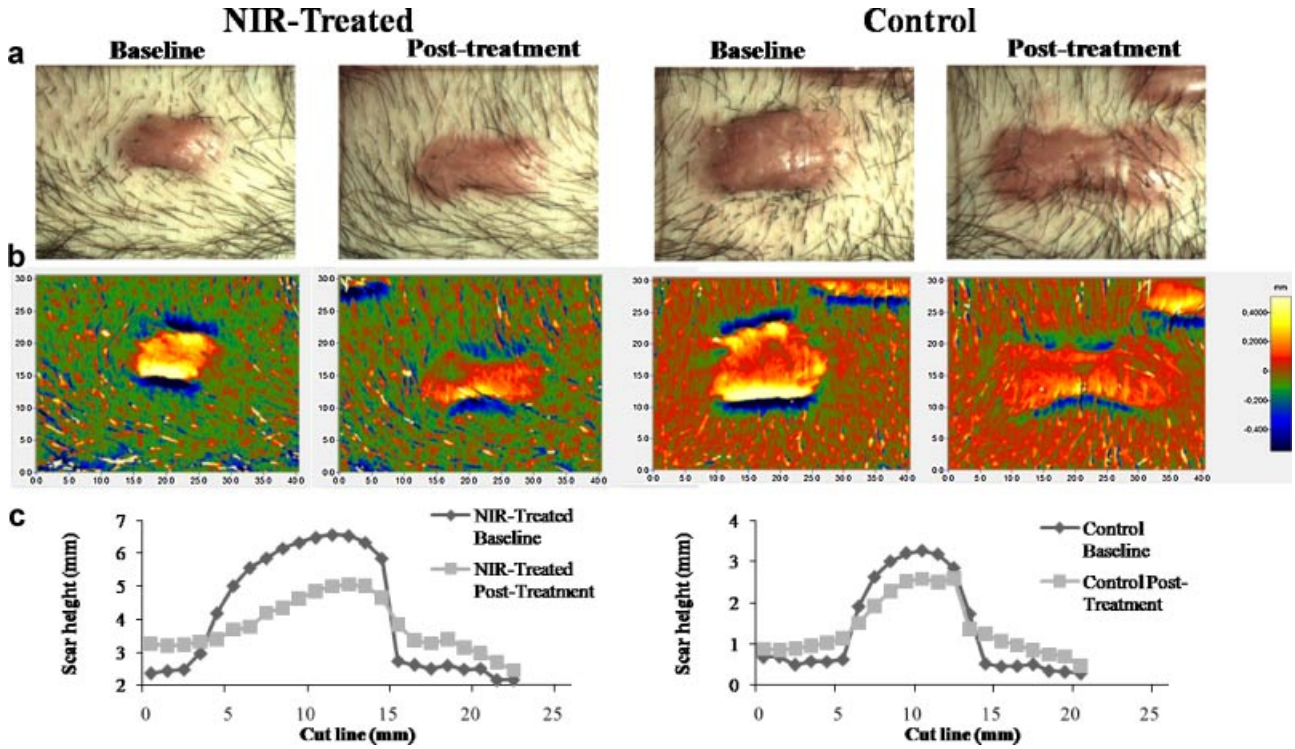

Fig. 2. Digital photographs (**a**) and PRIMOS color coded topographic images (**b**) obtained from Case 2 shows that there is a notable improvement in the scars height. This is represented by the increase of red to blue hue, and the loss of yellow hue. **c**: Cross-sectional representation of the scar height at baseline and post-treatment for the NIR-treated and control scars. Twenty-four points between these curves were compared to assess the overall mean improvement post-treatment in scar height for the NIR-treated and control scars. [Figure can be viewed in color online via www.interscience.wiley.com.]

derived growth factor (PDGF), interleukins (IL-6, 13, 15) and matrix metalloproteinases (MMPs) which are all also associated with (abnormal) wound repair [9]. Moreover, it has been shown that CO_2 therapy can reduce TGF-βI expression, which might have played a part in the overall effect in patients treated with this modality [7].

LED preconditioning with NIR irradiation was shown to reduce abnormal scars in our three patients, and may possibly become a clinically significant at home self-administered treatment modality. The results from the present case series are encouraging and underscore the need for controlled studies on a larger number of patients. Future trials should include long-term follow-up examinations to assess if results are maintained over time. Further studies are also necessary to identify the cellular processes underlying the therapeutic effects.

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REFERENCES

1. Wolfram D, Tzankov A, Pülzl P, Piza-Katzer H. Hypertrophic scars and keloids—A review of their pathophysiology, risk factors, and therapeutic management. Dermatol Surg 2009; 35(2):171–181.
2. Bock O, Schmid-Ott G, Malewski P, Mrowietz U. Quality of life of patients with keloid and hypertrophic scarring. Arch Dermatol Res 2006;297:433–438.
3. Bouzari N, Davis SC, Nouri K. Laser treatment of keloids and hypertrophic scars. Int J Dermatol 2007;46:80–88.
4. Louw L. The keloid phenomenon: Progress toward a solution. Clin Anat 2007;20:3–14.
5. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids. Plast Reconstr Surg 2010;125:557–568.
6. Liu W, Wang DR, Cao YL. TGF-b: A fibrotic factor in wound scarring and a potential target for anti-scarring gene therapy. Curr Gene Ther 2004;4:123–136.
7. Bouzari N, Davis SC, Nouri K. Laser treatment of keloids and hypertrophic scars. Int J Dermatol 2007;46:80–88.
8. Wolfram D, Tzankov A, Pülzl P, Piza-Katzer H. Hypertrophic scars and keloids—A review of their pathophysiology, risk factors, and therapeutic management. Dermatol Surg 2009; 35:171–181.
9. Hamblin MR, Demidova TN. Mechanisms of low level light therapy. In: Hamblin MR, Waynant RW, Anders J, eds. Proc of SPIE Vol. 6140. 2006; 614004.
10. Toyokawa H, Matsui Y, Uhara J, Tsuchiya H, Teshima S, Nakanishi H, Kwon AH, Azuma Y, Nagaoka T, Ogawa T, Kamiyama Y. Promotive effects of far-infrared ray on fullthickness skin wound healing in rats. Exp Biol Med (Maywood) 2003;228:724–729.
11. Danno K, Mori N, Toda K, Kobayashi T, Utani A. Near-infrared irradiation stimulates cutaneous wound repair: Laboratory experiments on possible mechanisms. Photodermatol Photoimmunol Photomed 2001;17:261–265.
12. Karu TI, Pyatibrat LV, Kolyakov SF, Afanasyeva NI. Absorption measurements of a cell monolayer relevant to phototherapy: Reduction of cytochrome c oxidase under near IR radiation. J Photochem Photobiol B 2005;81:98–106.
13. Morimoto Y, Arai T, Kikuchi M, Nakajima S, Nakamura H. Effect of low intensity Argon laser irradiation on mitochondria respiration. Lasers Surg Med 1994;15:191–199.
14. Yu W, Naim JO, McGowan M, Ippolito K, Lanzafame RJ. Photomodulation of oxidative metabolism and electron chain enzymes in rat liver mitochondria. Photochem Photobiol 1997;66:866–871.
15. Karu T. Photobiology of low-power laser effects. Health Phys 1989;56:691–704.
16. Zhang Y, Song S, Fong CC, Tsang CH, Yang Z, Yang M. cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light. J Invest Dermatol 2003;120:849–857.
17. Draaijers LJ, Tempelman FR, Botman YA, Tuinebreijer WE, Middelkoop E, Kreis RW, van Zuijlen PP. The patient and observer scar assessment scale: A reliable and feasible tool for scar evaluation. Plast Reconstr Surg 2004;113:1960–1965.