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Low level laser treatment of primary and secondary Raynaud's phenomenon

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Summary

Background: Patients who had been treated with low level laser (LLL) for their digital ulcers reported an impressive improvement of their symptoms of episodic digital ischaemia .Therefore this pilot study was performed to evaluate the efficacy of LLL as a new non-drug non-invasive treatment for patients with primary and secondary Raynaud's phenomenon (RP).

Patients and methods: Forty patients (29 female, 11 male, mean age 51 years) with active primary (28%) and secondary (72%) Raynaud's phenomenon received 10 sessions of LLL distant irradiation during winter months. Assessment of subjective and objective parameters was performed at baseline, one week after the last session and three months later. Variations of subjective parameters as number of daily acute episodes and severity of discomfort were assessed by a coloured visual analogue scale. A standardised cold challenge test using computed thermography of continuous temperature recordings by means of infrared telethermography was used to assess the digital blood flow.

Results: A significant improvement was noticed clinically and thermographically after 6 weeks and 3 months, respectively ($p < 0.0001$).

Conclusions: These data suggest that LLL treatment has a good short and medium term effectiveness in patients with Raynaud's phenomenon.

Key words

Raynaud's phenomenon, low level laser

Zusammenfassung

Einsatz des niederenergetischen Laser bei Patienten mit primärem und sekundärem Raynaud-Phänomen

Hintergrund: Das Raynaud-Phänomen ist eine intermittierend auftretende periphere akrale Zirkulationsstörung, deren Pathophysiologie noch nicht vollständig geklärt ist. Die Beobachtung eindrucksvoller klinischer Besserungen bei Patienten mit sekundärem Raynaud-Phänomen, welche wegen akraler Nekrosen mit dem Softlaser behandelt wurden, haben die Durchführung dieser Pilotstudie veranlasst.

Patienten und Methoden: Vierzig Patienten (29 Frauen, 11 Männer, mittleres Alter 51 Jahre) mit Raynaud-Symptomatik (28% primäres Raynaud-Phänomen, 72% sekundäres Raynaud-Phänomen) erhielten während der Wintermonate eine Behandlung mit dem Softlaser. Die Häufigkeit und Schwere der Raynaud-Attacken, beurteilt anhand einer analogen Farbskala sowie thermographische Parameter wurden zu Beginn, nach 6 Wochen und 3 Monaten beurteilt.

Ergebnisse: Sowohl die klinischen als auch die thermographischen Parameter waren nach 6 Wochen und 3 Monaten signifikant ($p < 0.0001$) gebessert.

Zusammenfassung: Die Ergebnisse dieser Pilotstudie sind sehr vielversprechend im Hinblick auf eine nichtpharmakologische Therapiemaßnahme bei Patienten mit Raynaud-Symptomatik. Der Stellenwert dieser Therapiemaßnahme sollte nunmehr im Rahmen einer randomisierten Studie definitiv evaluiert werden.

Introduction

Raynaud's phenomenon (RP) is an episodic peripheral circulatory disorder characterized by local artery vasoconstriction (spasm) in response to cold exposure or emotional stress [16]. The pathophysiology remains unresolved. However, there is an association between Raynaud's phenomenon and other vasospastic conditions, including migraine and variant angina suggesting that there may be a vascular defect common to these conditions [12]. Drug therapy for RP has several limitations, including lack of consistent response , development of tolerance with chronic use , and the development of numerous side effects such as dizziness, headache, palpitation, and orthostatic hypotension, many of which can be intolerable [3].

Low level laser treatment (LLL) has biostimulatory and regulatory effects and represents an athermic phototherapy utilizing light sources which emit low energy of usually red or infrared monochromatic light mainly used for acceleration of wound healing, and in pain therapy [1, 18]. We have observed that patients who had been treated with LLL for their digital ulcers reported impressive improvement of their symptoms of episodic digital ischaemia. Therefore this study was initiated to evaluate the efficacy of LLL as a new non-drug non-invasive treatment for patients with RP.

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Patients and methods

This prospective pilot study included 40 consecutive patients (29 female, 11 male), with active primary RP and secondary RP. Their characteristics are presented in Table I. Active RP was defined as episodes of digital blanching in response to cold or emotional stress, followed by cyanosis and/or rubor of fingers and/or toes. The diagnosis of primary RP was established by exclusion of associated diseases or known causes of RP (i.e. collagen vascular diseases, blood dyscrasias, neurologic disorders, vascular occlusive disease, or relevant drugs) [11]. Patients with systemic sclerosis (SSc) and rheumatoid arthritis (RA) fulfilled the American College of Rheumatology preliminary criteria. The underlying diseases of secondary RP are presented in Table II.

All patients had a history of 2 years or more and each patient had experienced at least 4 acute episodes of RP per week during the month preceding the study.

No vasodilator had been administered during this period.

Pregnant women and patients with severe cardiac or metabolic disorders were excluded. At baseline study visit, each patient provided a complete history and underwent physical examination. Blood chemistry measurements including immunological parameters (circulating autoantibodies, cold agglutinins and cryoglobulins), nail fold capillary microscopy [10], Doppler studies, shoulder girdle manœuvre, X-ray of the cervical spine and a nerve-conducting study were performed. All patients underwent a standardised cold-warm challenge test using computed thermography of continuous temperature recordings by means of infrared telethermography [6, 13, 14] at the following time intervals: a) basal finger tip skin temperature after being adapted to room temperature for about 20 minutes, b) immediately after 1 minute warm challenge (immersion of gloved hands in water at 39°C), and c) measurements immediately after 1 minute cold challenge (immersion of gloved hands in water at 20°C). Recovery temperatures were measured 10 and 20 minutes later. The room temperature was 22.0 ± 0.5°C. We used 20°C for 1 minute, as proposed by Ring, since colder temperatures can lead to extended recovery times and may be painful [13, 14].

At the beginning of the trial, patients received an instruction booklet and a clinical diary for recording variations in subjective symptoms. The study was performed during the winter (between November 99 and March 2000) the average minimum temperature during the trial period – provided by the Zentralanstalt für Meteorologie und Geodynamik in Vienna, was the following : November 99 1.9°C, December 99–0.7°C, January 2000–0.9°C, February 2000 1.9°C and March 2000 3.2°C.

Table I: Demographic data.

	Primary RP (n = 11) 28%	Secondary RP (n = 29) 72%
Median age, years	59 (*33–69)	56 (*40–60)
Male sex (%)	4 (31%)	7 (26%)
Median duration of RP, years	8 (*5–14)	10 (*4.5–12.5)

* IQR: interquartile range.

Table II: The underlying diseases of the secondary Raynaud's phenomenon (SRP) in the study population.

	No of patients
Systemic sclerosis (SSc)	10
CREST	1
Systemic lupus erythematosus (SLE)	1
Rheumatoid arthritis (RA)	1
Undifferentiated collagenosis	13
Carpal tunnel syndrome (CTS)	3

Intervention

Each patient received 10 sessions of low level laser distant irradiation treatment by means of a 250 mW, 670 nm continuous wave diode laser (Helbo Laser, Grieskirchen, Austria), 1000 sec per session, intensity 250 mW, power density 1.1 mW per square cm applied to the palms and fingers of both hands simultaneously. The machine was standardised initially, and the output was controlled regularly. The first 3 sessions were performed during the first week every other day, 7 further sessions were performed twice weekly.

Follow-up: Variations in subjective and objective parameters that occurred during the trial were assessed again one week after the last session (6 weeks after the first session) and three months later. Variations of subjective parameters as number of daily acute episodes and severity of discomfort was assessed by means of a coloured 10 cm visual analogue scale (VAS) with 0 representing minimum and 10 representing maximum [7]. Telethermography pre and post cold-warm challenge was used to assess the digital blood flow.

Statistical methods

Continuous data are presented as the mean and 95% confidence intervall (95% CI) or if adequate as the median and the interquartile range (range from the 25th to the 75th percentile). Percentages were calculated for dichotomous variables. For comparison of baseline data and follow-up data paired t-tests were used. The Mann-Whitney-U-test was used to compare the change of VAS score one week and 3 months after LLL treatment between patients with primary and secondary Raynaud phenomenon. A p-value of 0.05 was considered statistically significant. All calculations were performed with SPSS (Version 10.0).

Results

Analysis of subjective variation of patient complaints measured by VAS revealed that one week after end of treatment 23 (58%) patients completely recovered (VAS 0). Overall there was a significant reduction of subjective discomfort according to the pre- and post- treatment VAS

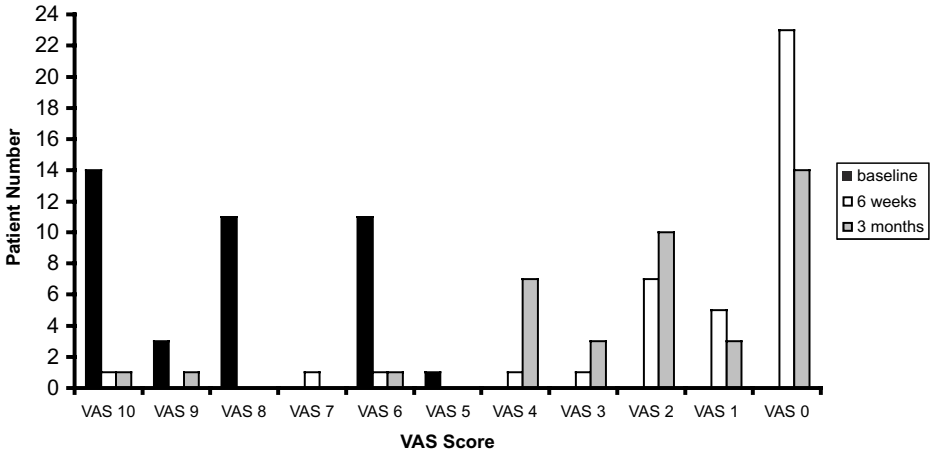

Fig. 1: Visual analogue scale (VAS) of the frequency and severity of Raynaud's phenomenon of all patients; at baseline, 6 weeks and three months after laser treatment.

scores ($p < 0.0001$). Only one patient described no subjective improvement after this time period. Three months after treatment 14 (35%) patients remained without complaints (VAS 0). Overall reduction of discomfort remained significant after this time period ($p < 0.0001$). No significant differences in the improvement of patients with primary and secondary RP was found at one week after the end of treatment ($p = 0.7$) and 3 months ($p = 1.0$) after LLL treatment. VAS scores of all patients at baseline, one week after treatment and 3 months after treatment are shown in Figure 1. The results of both subgroups primary and secondary RP are presented in Table III.

Thermographically one week after treatment 17 (42%) patients (8 with primary RP and 9 with secondary RP) had completely normal findings on cold-warm challenge test as these patients had no delayed recovery phases after cold exposure. In all 40 patients a significant increase of the recovery temperature after cold exposure 6 weeks after the begin of the laser treatment compared to the pre-treatment values was found ($p < 0.0001$).

No side-effects of any kind were noted. Although therapy was applied only to the palms and fingers of both hands, improvement also occurred in patients in whom the toes were mainly affected. These data suggest that LLL treatment has a good short and medium term effectiveness in patients with RP.

Discussion

Dysfunction of the peripheral vascular tone control is mainly caused by derangement of endothelium and of the peripheral nervous system [5]. Studies have suggested that changes in the nervous system at either the peripheral level or central level, are always linked to profound abnormality of endothelial function [5].

Table III: Median and interquartile range (IQR) of the visual analogue score (VAS) of the patients with primary and secondary RP, at baseline, 6 weeks later and three months after laser treatment.

RP	VAS score at baseline	VAS score 6 week later	VAS score three months later
primary	8 (6 to 9)	0 (0 to 2)	1 (0 to 3)
secondary	8 (7 to 10)	0 (0 to 2)	2 (0 to 4)

The endothelial cell modulates vascular tone by releasing vasoactive substances that promote either vessel wall dilation or constriction. The vasodilator substances are nitric oxide, prostacyclin, bradykinin and endothelium-derived hyperpolarizing factor [9]. Activated endothelial cells balance the vasodilator effects of those peptides by synthesizing vasoconstrictor peptide endothelin-1, which promotes concentration-dependent contractions that are slow to develop and long-lasting [9]. Digital cutaneous neurons show a deficient release of vasodilatory calcitonin gene related peptide in primary RP [17]. Moreover an impairment of endothelium-dependent dilatation in veins of patients with RP has been reported [2].

Biological responses of cells to visible and near-IR (laser) radiation occur due to physical and/or chemical changes in photoreceptor molecules, components of respiratory chains like cytochrome c oxidase and NADH-dehydrogenase. As a result of the photoexcitation of electronic states, the following changes occur: increase of ATP production, alteration of redox properties and acceleration of electron transfer, changes in biological activity due to local transient heating of chromophores, NO release from inhibitive position in cytochrome c catalytic centre, and one-electron auto-oxidation and O_2^- (and subsequent production of H_2O_2), photodynamic action and $^1O_2$ [8]. LLL vitalizes the cells by increasing the mitochondrial ATP (adenosine-triphosphate)-production [19]. ATP induces vasodilation which may be not mediated by nitric oxide [15]. LLL might improve the endothelial function in patients with RP. Indeed, we could demonstrate in our laboratory that the flow dependent, endothelium-mediated dilatation of the brachial artery in patients with primary RP can be improved by laser therapy [4]. The results of this pilot study have to be confirmed in a randomised double-blind study. Such a study was initiated in our department.

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