Low Level Laser Therapy in Primary Raynaud's Phenomenon — Results of a Placebo Controlled, Double Blind Intervention Study

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ABSTRACT. ***Objective.*** To assess the efficacy of low level laser therapy in patients with primary Raynaud's phenomenon and predict the success of laser therapy by clinical characteristics.

Methods. Forty-eight patients were included in a randomized placebo controlled, double blind crossover study. Laser and sham therapy each were applied 5 days a week for 3 weeks. Clinical symptoms, exposure to triggers, and frequency and intensity of attacks were recorded in diaries. Results of infrared thermography before onset and at the end of both irradiation sequences were evaluated. Primary endpoint was the average intensity of attacks; secondary endpoints were average number of attacks and thermography results. Age, sex, duration of symptoms, age at onset of symptoms, evoking conditions other than cold, maximum temperature drop after cold provocation, and rewarming time after cold provocation were tested as potential predictors.

Results. Number of attacks and their intensity were significantly reduced during laser therapy compared to sham treatment. Thermographic parameters did not reach statistical significance. In a stepwise multiple regression analysis, evoking conditions other than cold (stress, wetness as additional triggers), rewarming time, and temperature decrease after cold provocation were significant predictors of therapeutic efficacy.

Conclusion. Low level laser therapy reduces frequency and severity of Raynaud attacks. The effect is most pronounced in patients with signs of decreased threshold for vasospasm and less effective in patients with delayed hyperemia. (J Rheumatol 2004;31:2408–12)

Key Indexing Terms:
RAYNAUD'S DISEASE LASER THERAPY LOW LEVEL

Causal therapy of a disease is only possible if the underlying pathogenetic mechanisms are known. This is not fully the case in primary Raynaud's phenomenon (RP). Several mechanisms, such as altered sympathetic nervous system activity or a local defect of digital vasculature including endothelium dependent vascular regulation and the role of prostacyclins, nitric oxide, and endothelin–1, have been discussed, but other factors like calcitonin gene related peptide and nonvascular factors[1-5] have also been suggested. However, the complete causal chain remains unknown, as implied by its name.

Principally, all the above aspects of the pathogenetic mechanism are targets for therapeutic intervention. Proposed therapies include a wide range, from application of vasodilative drugs to surgery[6,7]. Some therapies originate from clinical experience and experimental evidence, but lack an established mechanism of action. Low level laser therapy (LLLT) falls into this category, although biological effects at a vascular level have been demonstrated experimentally[8].

Regarding the clinical efficacy of LLLT, only a few reports may be considered for an evidence based approach[9–11]. Based on a previous placebo controlled, double blind study[9], we report the results of an extended clinical trial. As a question of special interest the study also assessed whether success of laser therapy is predictable from clinical and other characteristics of patients with primary RP.

MATERIALS AND METHODS

Patients and diagnostic procedure. Patients were enrolled during the cold season (November to March) of the years 2001 to 2003. All subjects falling into the diagnostic category and presenting at our outpatient unit were asked to take part until the predetermined number of patients (n = 50) was reached. Patients gave informed consent. Refusals (26%) were mainly due to time constraints of patients. Two patients had incomplete data sets and were excluded from evaluation.

Patients were eligible if they were diagnosed with primary RP according to the diagnostic criteria outlined below and were not currently taking vasoactive medication that could interfere with vascular response.

Primary RP is defined as episodic ischemia of the digits clinically characterized by blanching, cyanosis, and frequently rubor of the skin in

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response to cold exposure or emotional stimuli unassociated with other diseases[12].

Before starting the trial a standardized diagnostic procedure[13] was performed to exclude patients with suspected secondary RP. Only patients with persisting symptoms were included. The procedure allows exclusion of cases of secondary RP with high probability. It consists of a screening and extended diagnostic program. The screening program consists of the following steps: (1) Patient's history and demographic criteria. (2) Clinical examination (palpation of limbs, Allen's test, signs of connective tissue disease). (3) Noninvasive angiologic examination (Doppler sonography, acral oscillography, microscopy of nailfold capillaries). (4) Radiographic examination (chest, both hands). (5) Laboratory chemistry studies (Westergren sedimentation rate, differential blood count, renal function, and serological markers).

Patients with screening results in keeping with suspected secondary RP were subjected to the extended diagnostic program consisting of either an aortic arch angiography or a specific test program designed to establish the underlying disease (organ screening) that was tailored to the findings during the screening program and further tuned according to the findings collected during the extended program.

To objectively assess vasospasms an electronic amplified acral oscillography was performed[14]. Oscillography was done on all fingers of both hands in resting position. Oscillograms were inspected for indications of spasm both spontaneously after warm (5 min in water at 37°C) and cold provocation (5 min in water at 12°C) and 1, 3, 5, 7, 10, 12, 15, 17, and 20 minutes after cold provocation. At the same timepoints skin temperature measurements were taken. Based on these data, the timepoint of absence of vasospasm and rewarming time were calculated by determining the intersection of the temperature curve with the straight line drawn from the temperature before cold provocation. Additionally, the maximum drop in skin temperature after cold provocation was determined.

Experimental procedure. Two devices with identical appearance were available (Heltschl GmbH, Schlüsslberg, Austria). Device A was a diode laser (power 200 mW, wavelength 685 nm), device B was a noncoherent light emitting diode (power 200 mW, wavelength 640–685 nm). Both systems were controlled by identical panels. Focus for the laser device was set to 2 J/cm^2 by adjusting exposure duration to the size of the irradiated area. The light source was placed on the top side of a box specifically constructed for the purpose of this study. Patients put their hands into 2 slots to standardize position of the irradiated area and to obscure the light emitted by the arrays. The irradiated area was the fingers and back of the hands. Duration of exposure was 30 to 40 minutes.

Each therapeutic sequence had a duration of 3 weeks with 5 sessions per week. After this sequence the device was changed and another 3-week sequence was started. The initial device was randomly selected. Neither the investigators nor the clinical staff or patients knew which of the devices labeled A and B were the laser or the sham exposure device. The sequence of experimental conditions was completely balanced.

Two weeks before the start of irradiation, during the 6 weeks of exposure sessions, and for 2 weeks posttreatment, patients were instructed to record any Raynaud attacks in diaries. These diaries were small booklets with columns for each day. Type and number of exposures to attack-provoking situations and number of attacks had to be recorded daily at bedtime. This information was used to calculate the relative frequency of attacks. Average intensity of attacks was scaled weekly on a 5-point category scale (1 = minimal, 5 = severe). This procedure was chosen based on our prior experience with Raynaud diaries, where the bedtime entry method proved superior to on-the-spot entries. The main reasons for problems experienced with the latter type are the following: Many attacks occur outside, often during rain or snow, conditions when it is difficult to fetch the booklet and pencil and make an entry; during attacks it is difficult for patients to use a pencil anyway, if the attack occurs on the dominant hand as is often the case; often the booklets got lost, or strictly speaking, blown away, when patients carried them around all the time.

At the beginning, after the first 3 weeks, and after the second 3-week period, infrared thermography (NEC San-ei Thermotracer) was applied after local cooling. Infrared thermography appears to be suitable for evaluating effects especially in patients with vascular and rheumatic diseases[15,16]. In brief, the procedure was as follows: After adaptation to a room temperature of 24°C with arms undressed for at least 15 minutes, patients put their palms on a plastic covered panel for measurement of the baseline thermogram. Next, patients put on plastic gloves and for 1 minute placed their hands into a basin of water kept at a temperature of 20°C. Recovery was measured immediately afterwards and during the first 20 minutes after cold exposure. For thermographic evaluation, circular regions of interest at the fingertips and at the center of the metacarpal bones were selected. Temperature gradients were calculated for each finger as differences between temperature readings from metacarpus to finger. A negative difference exceeding 1 centigrade degree was considered pathological. The mean temperature gradient of all fingers of both hands 20 minutes after exposure to cold water was used as an indicator of general vasospastic conditions. Additionally, the number of fingers showing a temperature difference between metacarpus and finger in excess of 1 centigrade degree at 20 minutes after cold exposure was counted as an indicator of a pathological temperature gradient.

The primary endpoint was defined as the average intensity of Raynaud attacks during the 3-week application of either laser or placebo treatment. For identifying potential predictors of responsiveness to laser therapy, the relative difference in average intensity of attacks during laser and placebo treatment relative to the pretreatment intensity of attacks was used as criterion. Secondary endpoints were the average number of attacks and the results of infrared thermography.

Statistical methods. Comparison of laser and placebo conditions was done by ANOVA, controlling for sequence of conditions. Data for each week were included and constitute a third factor in addition to laser versus placebo and sequence of conditions. Rather than pooling data over the whole period this procedure was chosen to assess potential differences in time trends across experimental conditions. Normality was assessed by Kolmogorov-Smirnov tests.

Multiple linear regression analysis was applied to test whether responsiveness to laser therapy can be predicted by characteristics of patients. Age, sex, duration of symptoms, age at onset of symptoms, evoking conditions other than cold, maximum temperature drop after cold provocation, and rewarming time after cold provocation were tested as potential predictors.

RESULTS

A total of 48 patients with primary RP, 38 women and 10 men, were included. Mean age (± SD) was 46 ± 14 years and age at onset of symptoms was 26 ± 11 years; duration of symptoms was 20 ± 10 years. Conditions evoking symptoms were cold (100%), wetness (63%), and stress (33%). In all patients, more than one finger of both hands was affected and in 23% the toes as well.

As shown in Table 1, frequency of exposure to evoking conditions (cold, wetness, etc.) did not differ between pretreatment phase and laser or placebo therapy period (3 weeks each). An average of 3 such exposures were reported per day. Ambient temperature as recorded by the meteorological monitoring station was statistically not different between sham and laser exposure periods (sham 3.2 ± 3.6°C; laser 3.0 ± 3.9°C).

Both the number of attacks and their intensity were significantly reduced during the period of laser therapy compared to sham treatment regardless of whether the absolute number of attacks or their relation to the number of attack-

Table 1. Mean ± SD of average number of exposures per day, attacks per day (absolute and relative to number of exposures), intensity of attacks (5-point scale, minimal to severe; absolute and relative to week preceding treatment phase) for each week of laser and placebo treatment.

		Laser			Placebo			
	Pre	1st	2nd	3rd	1st	2nd	3rd	p
Exposure	3.0 ± 1.7	3.0 ± 1.8	2.9 ± 1.5	2.9 ± 1.5	2.9 ± 1.6	3.0 ± 1.4	2.9 ± 1.6	0.881
Attacks	2.5 ± 1.5	1.8 ± 1.3	1.6 ± 1.0	1.6 ± 1.0	2.1 ± 1.2	2.2 ± 1.3	2.0 ± 1.2	0.001
Attacks relative to exposure*	90 ± 41	72 ± 52	66 ± 42	66 ± 42	83 ± 57	82 ± 52	78 ± 46	0.008
Intensity	3.2 ± 1.2	2.5 ± 0.9	2.3 ± 0.9	2.3 ± 1.0	2.9 ± 1.2	2.8 ± 1.0	2.8 ± 1.1	< 0.001
Intensity relative to pretreatment*		87 ± 44	80 ± 37	78 ± 36	96 ± 39	96 ± 43	94 ± 34	< 0.001

p value from ANOVA for comparison of laser and placebo.* Within ANOVA, values were arcsine-transformed.

evoking exposures was tested. A slightly reduced frequency of attacks was also seen during sham treatment; however, reduction was significantly higher during the laser therapy period. Intensity of attacks was only slightly reduced during placebo phase (about 96% of pretreatment intensity), while laser therapy resulted in a highly significant reduction to about 82%, with a decreasing trend during the 3-week therapy period.

Although all thermographic measures compared favorably for laser therapy, none of them reached statistical significance (Table 2).

To determine a possible role of clinical and other characteristics of the patients with respect to responsiveness to laser therapy, the reduction of the intensity of Raynaud attacks was analyzed with respect to age, sex, age at onset of symptoms, duration of symptoms, provoking conditions, regions affected (fingers, toes), maximum temperature drop after cold provocation, and rewarming time after cold provocation. A stepwise multiple regression revealed that only wet conditions as an additional provoking condition, rewarming time, and temperature decrease after cold provocation showed a significant relationship to the criterion of reduction of intensity of attacks (Table 3). Subjects experiencing evoking conditions other than cold (stress, wetness) and/or having a long rewarming time and/or experiencing a less pronounced temperature drop after cold provocation show a reduced effect of laser therapy.

DISCUSSION

In principle, primary RP is a benign disease; however, complaints may be severe, quality of life is reduced, and patients may be restricted in their occupational functions. Average Raynaud attacks last about 25 minutes and several such attacks per day limit social activities and sometimes force patients to stay indoors[17]. The main diagnostic challenge is differentiation between primary and secondary RP. Therapeutic intervention in primary RP is limited and restricted mainly to counseling in prophylactic avoidance of exposure to evoking stimuli. If this is unsuccessful, medication is usually prescribed, although the balance between potential benefit and adverse effects is frequently suboptimal.

This limited therapeutic spectrum leads to increased awareness for alternative therapeutic methods. One of these methods is LLLT. LLLT has been used in patients with vascular or rheumatic diseases; however, its effects are not unambiguous[18,19].

The reasons for exploring the use of LLLT in patients with primary RP were anecdotal evidence and first experience with this method at our outpatient unit. This led to the development of a study protocol using each subject as his/her own control and thus showing a good potential to detect any possible effect, while simultaneously controlling for confounding conditions by using a sham treatment and crossover approach.

Essentially, the results of a previous pilot study were replicated[9]. Frequency of attacks was only slightly reduced in the previous study, although based on less than one-third of the number of patients in the present trial. Clinical indicators of relevance for the patients' well being, such as frequency and intensity of attacks, were substantially reduced by LLLT. Frequency of attacks was reduced by about 20%. Mean reduction of intensity of attacks by 0.5 to 1 scale points is also of clinical significance, as it amounts to a

Table 2. Results of infrared thermography: means ± SD of finger-metacarpus temperature difference averaged over all fingers, maximum temperature difference, and number of fingers with pathological gradient.

	Pre	Laser	Placebo	p
Mean gradient	–1.29 ± 1.75	–0.64 ± 1.09	–1.10 ± 1.83	0.130
Maximum gradient	–2.36 ± 1.96	–2.27 ± 1.68	–2.77 ± 1.80	0.248
Number of fingers < 1 centigrade degree	4.94 ± 4.31	3.84 ± 4.13	4.32 ± 4.50	0.295

p value from ANOVA for comparison of laser and placebo, except number of fingers tested by Wilcoxon test.

Table 3. Standardized regression coefficients for evoking conditions other than cold (stress, wetness), rewarming time, and temperature decrease after cold provocation as predictors of responsiveness to laser therapy (difference of intensity of attacks between laser and placebo related to pretreatment intensity). Multiple R = 0.51.

Predictor	Standardized Regression Coefficient	p
Evoking conditions	–0.294	0.097
Rewarming time	–0.432	0.016
Temperature decrease	0.371	0.035

decrease of 15 to 35 percentile points (depending on baseline intensity). Similar results have been obtained in a placebo controlled study of RP, however, with a predominance of patients with secondary RP[11]. The effect reported in this study was even more pronounced, which may be due to differences in the definition of study groups (with and without secondary RP) and different study designs leading to different placebo effects.

In the recently published study[11], a significant improvement was also shown for infrared thermography. In our study only insignificant changes were found, which may be due to poor reproducibility of infrared thermography in patients with RP[20] and differences in the evaluation method applied.

Analysis of factors that may allow prediction of the effectiveness of LLLT revealed that patients with cold as the only trigger, and patients with more pronounced temperature decrease after cold provocation and/or shorter rewarming time showed a more favorable response to LLLT. The differential effectiveness of LLLT suggests an intrinsic heterogeneity of the clinical presentation of primary RP. Detailed evaluation of acral oscillograms after cold provocation revealed 2 distinct reaction types (with few patients showing a mixture of both): one characterized by immediate vasospasm accompanied by a pronounced decrease of temperature, but followed by a comparably sharp temperature increase; the other with a slower onset and less pronounced drop of temperature, but with prolonged delay of reactive hyperemia. Considering the discussion on endothelium-dependent and independent pathways of vasoregulation and their role in RP[4-6,21-25] and the results regarding the differential benefit of LLLT, we propose the hypothesis that the effects of laser therapy are based on an endothelium-independent mechanism. It may be hypothesized that LLLT acts by an influence on peripheral adrenergic nerves and postsynaptic alpha receptors, in accord with the assumption that LLLT changes cell membrane permeability[26].

Apart from purely scientific interest in alternative therapeutic approaches, a shortage of available resources makes it imperative to assess clinical effectiveness of such alternative methods objectively. Such therapeutic methods may only gain importance in clinical practice if supported by an evidence-based perspective. While the slightly beneficial effects of placebo therapy may be considered as indicating the positive expectations of patients, these effects failed to reach statistical significance, and the difference of LLLT was substantial, emphasizing a true therapeutic effect of laser therapy. This also serves to underline the importance of controlled and double blind trials, especially in cases requiring subjective assessment as in the case of primary RP.

It has been shown that LLLT reduces intensity and frequency of attacks of Raynaud's phenomenon. Differential therapeutic effects were observed in patients experiencing differing intensity of vasospasms and degree of suppression of reactive hyperemia after cold provocation. Whether this is due to endothelium-independent factors remains to be elucidated. Further, by an *ex iuvantibus* argument based on this differential effect of LLLT, an intrinsic heterogeneity of primary RP is suggested, which if substantiated in future investigations may help clarify the pathogenetic mechanism of primary RP.

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