Rheumatol Int
DOI 10.1007/s00296-011-1882-2

SHORT COMMUNICATION

Effect of biofeedback and deep oscillation on Raynaud's phenomenon secondary to systemic sclerosis: results of a controlled prospective randomized clinical trial

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Received: 21 December 2010 / Accepted: 18 February 2011

Abstract Our aim was to evaluate the effect of deep oscillation and biofeedback on Raynaud's phenomenon (RP) secondary to systemic sclerosis (SSc). A prospective randomized study was performed in SSc patients receiving either deep oscillation ($n = 10$) or biofeedback ($n = 8$) thrice a week for 4 weeks, or patients were randomized into the waiting group untreated for vasculopathy ($n = 10$) in time of running the study interventions. Biofeedback resulted in an improvement of RP as determined by score reduction of visual analogue scale compared with patients of the control group ($P < 0.05$), whereas deep oscillation revealed a tendency for improvement ($P = 0.055$). The study underlines the beneficial role of physiotherapy for the treatment of SSc-related RP.

Keywords Biofeedback · Raynaud's phenomenon · Deep oscillation · Systemic sclerosis · Physiotherapy

Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterized by proliferative and obliterative vasculopathy. Raynaud's phenomenon (RP) as an initial and characteristic feature of SSc may represent direct triggers for the fibrotic processes, ulcerations, and progression to gangrene. [1, 2]. Therefore, reduction in the frequency and severity of RP is an important target of therapy. Several drugs are currently used to treat RP [3], despite their very limited effects and potentially adverse side effects. As recently described, infrared-mediated hyperthermia as physiotherapy showed positive effects on scleroderma-associated RP [4]. Deep oscillation is used as an additional therapy of lymphoedema and can supplement manual lymphatic drainage. Often it is also used in patients with SSc [5]. However, the effect of this therapy on RP has not been proven so far. In contrast, use of biofeedback as a behavioural treatment has been suggested to be effective in RP secondary to different connective tissue diseases by a retrospective analysis [6] and in advanced SSc [7, 8]. Despite these promising results, no prospective randomized controlled studies have been published so far.

Materials and methods

Patients

Twenty-eight patients fulfilling the ACR criteria for SSc and suffering from RP were randomized by staff unaware of any clinical data for either biofeedback ($n = 8$), deep oscillation ($n = 10$) or no intervention or therapies with an expected effect on vasculopathy ($n = 10$).We used this group for placebo as sham procedure is not satisfactory feasible.

Demographic data are shown in Table 1. Written informed consent was obtained from each patient to participate in this study. The study was approved by the local

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Published online: 08 April 2011

ethics committee (EA 1/100/05), conducted between October 2004 and February 2008, and was announced as clinical trial (NCT00946738).

Study design

Deep oscillation providing a pulsing electromagnetic field (5–200 Hz) was performed thrice weekly for 4 weeks [5]. Biofeedback was performed with the same frequency and duration as deep oscillation [6, 7]. Primary outcome was measured as change in the scleroderma-VAS for Raynaud's phenomenon. The scleroderma-VAS includes five scales that assess Raynaud's symptoms and digital ulcers, gastrointestinal symptoms, shortness of breath and overall disease severity. Patients were asked to indicate how much these problems have interfered with activities. In addition, patients underwent laboratory cold stress tests during which they were instructed to maintain digital temperature as the ambient temperature was slowly dropped from 25 to 17°C. Patients were assessed at baseline, at the end of treatment at week 4 and at long-term follow-up at week 12.

Statistics

Statistical analysis was performed using SPSS V16.0 statistical package. Kruskal–Wallis tests, with post hoc group-wise tests, were performed on absolute and relative score differences between the measurement points and baseline to identify different treatment effects between the groups after 4 and 12 weeks.

Regression analyses were subsequently performed to verify significant influences of biofeedback and deep oscillation on treatment response in a multivariate setting including potential confounders. We used linear regression analysis to model an equation for calculating the absolute score change between a measurement point and baseline. Score at baseline, age, gender, disease duration, modified Rodnan Skin Score (mRSS) at baseline, smoking status and season at the time of measurement were accounted as confounders. Therefore, using an additive regression model, multi-categorical variables were dichotomized for better interpretation of the analysis. So if the considered dichotomized feature is fulfilled, resulting factors from the

Table 1 Epidemiologic characteristics of the patients

	Total	Deep oscillation	Biofeedback	Control	*P* value
Number of patients	28	10	8	10	
Female	24 (85.7%)	8 (80.0%)	7 (87.5%)	9 (90.0%)	0.804[c]
Age in years (mean ± SD)	54.4 ± 11.3	53.4 ± 11.6	50.0 ± 15.1	58.9 ± 5.3	0.242[a]
Disease duration in years, median (range)	4.0 (25.0)	4.0 (25.0)	6.0 (16.0)	1.5 (7.0)	**0.013**[b]
Type of SSc					0.148[c]
Diffuse	9 (32.1%)	5 (50.0%)	3 (37.5%)	1 (10.0%)	
Limited	19 (67.9%)	5 (50.0%)	5 (62.5%)	9 (90.0%)	
MRSS, median (range)	5.5 (23)	8.0 (19)	4.0 (14)	5.5 (11)	**0.028**[b]
Valentini score (mean ± SD)	1.4 ± 0.8	1.6 ± 0.9	1.3 ± 0.6	1.3 ± 0.8	0.733[a]
ANA positive	24 (85.7%)	9 (90%)	7 (87.5%)	8 (80.0%)	0.804[c]
Anti-Scl70 ab positive	4 (14.3%)	2 (20%)	2 (25.0%)	0	0.261[c]
Anti-centromer ab positive	11 (39.3%)	5 (50%)	2 (25.0%)	4 (40.0%)	0.558[c]
Smoking status					0.304[c]
Ex-smoker	2 (7.1%)	1 (10.0%)	0	1 (10.0%)	
Smoker	2 (7.1%)	0	0	2 (20.0%)	
Physiotherapy prior to study	18 (69.2%)	7 (70.0%)	5 (62.5%)	6 (75.0%)	0.343[c]
Baseline scores on scleroderma-VAS (VAS 0–10), median (range)					
Raynaud's phenomenon	6.0 (8.6)	6.5 (8.2)	4.9 (8.6)	3.8 (7.5)	0.312[b]
Ulcers	2.8 (9.9)	5.6 (9.9)	0.5 (9.6)	3.1 (6.0)	0.394[b]
General disease symptoms	5.9 (9)	6.9 (9.0)	2.4 (8.4)	5.3 (6.5)	0.108[b]
Season of initiation of therapy					0.775[c]
Spring	5 (17.9%)	3 (30%)	1 (12.5%)	1 (10%)	
Summer	6 (21.4%)	2 (20%)	1 (12.5%)	3 (30%)	
Autumn	8 (28.6%)	3 (30%)	2 (25.0%)	3 (30%)	
Winter	9 (32.1%)	2 (20%)	4 (50.0%)	3 (30%)	

P values <0.05 (significant) are in bold

[a] ANOVA; [b] Kruskal–Wallis test; [c] Chi^2 test

linear regression analysis represent the associated score change. Assuming in addition to a general effect of the vasculopathy treating physical therapies over the control a possible superiority of one treatment over the other, 'therapy' was dichotomized into the two new variables 'oscillation' and 'biofeedback'. Since case numbers were rather low for a multivariate analysis, regression was performed with both forward (variables with predictive value are stepwise entered into the equation) and backward selection (equations start with all variables included and variables with missing predictive value are stepwise eliminated) to verify selection results.

Results

At baseline, the three groups did not differ significantly apart from disease duration and mRSS score (Table 1). Concerning the score for RP (Fig. 1) in treatment response 4 weeks after initiation of therapy, the three groups showed significant differences (score difference from baseline absolute $P = 0.032$, relative $P = 0.017$). Biofeedback resulted in a significant improvement of RP compared to control patients (score difference absolute $P = 0.021$, relative 0.014). Deep oscillation also exhibited improvement in the group-wise comparison with the control group but only showed a statistical tendency (absolute score difference from baseline $P = 0.055$, relative difference $p = 0.050$). The score changes for ulcers and general disease symptoms did not differ between the 3 groups.

Despite randomization, there were differences in the baseline score for Raynaud's phenomenon. Therefore, we displayed both absolute and relative changes in Fig. 1, assuming that patients with a lower baseline score had less potential to reduce their score than patients with a higher initial score. Hence, the change should be evaluated under consideration of these different baseline conditions. The considerable box overlap of oscillation and biofeedback for absolute changes at week 12 looks different when comparing relative changes—suggesting that the biofeedback group started with lower baseline scores which led to the more prominent relative decrease.

Subsequently, these treatment effects for the score change of RP were verified in a multivariate setting. Score at baseline, gender, disease duration, mRSS at baseline and smoking status had no confounding influence. Forward and backward regression selection delivered the same results for week 4 and slightly different results for week 12 (Table 2) but led to the same conclusions: at the end of treatment, both therapies showed an improvement by contributing remarkably to a score reduction from baseline to week 4 and even week 12.

At week 4, the regression results for the absolute score difference at week 4 were similar for both selection methods: the average score increase over all three treatment groups on scleroderma-VAS for RP between week 4 and baseline was calculated as 6.891. This score increase is decreasing with rising age (with each year by −0.093). In addition to that age effect, we saw a score reduction by −3.822 when a patient got biofeedback which was almost double the effect of deep oscillation (−1.969). At long-term follow-up at week 12, as expected, change of the RP score also seemed to be influenced by season of measurement (summer −2.191 in the forward selection model, winter +1.130 in the backward selection model).

The ability of patients to maintain digital temperature during the cold stress challenge showed no significant differences 4 and 12 weeks after initiation of therapy.

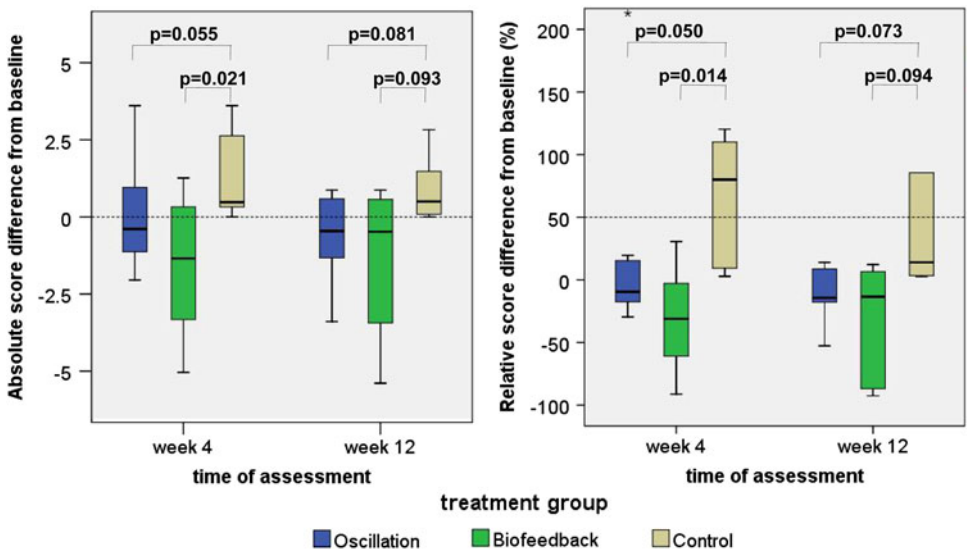

Fig. 1 Score changes from baseline as absolute and relative differences for Raynaud's phenomenon assessed by scleroderma-VAS 4 and 12 weeks after initiation of therapy

Table 2 Regression analyses were performed to verify significant influences of biofeedback and deep oscillation on treatment response (absolute score change from baseline)

Follow up Regression selection method	Week 4 Forward = Backward	Week 12 Forward	Backward
Constant	6.891	0.817	6.769
Age	−0.093		−0.108
Physiotherapy (0/1)			
Oscillation	−1.969		−1.741
Biofeedback	−3.822	−1.843	−3.114
Season at measurement (0/1)			
Spring			
Summer		−2.191	
Autumn			
Winter			1.130

Since case numbers were rather low for a multivariate analysis, regression was performed with both forward and backward selection to verify selection results. Positive values indicate a mean increase (i.e. worsening) of the score, and negative values a decrease

i.e. models resulting from the forward selection

Score difference (week 4-baseline) = 6.891–0.093 * age −1.969 * oscillation −3.822 * biofeedback

Score difference (week 12-baseline) = 0.817–1. 843 * biofeedback−2.191 * measurement-in-summer

Discussion

Studies examining the effectiveness of the physiotherapy and rehabilitation for the management of Raynaud phenomenon secondary to SSc are infrequent and important. Prior studies make contradictory statements on this, partly due to inconsistent study designs [9].

In our clinical practice, we use deep oscillation in the therapy of swelling due to lymphedema and SSc as a supplement of manual lymphatic drainage. In case of secondary lymphedema due to surgical treatment of breast cancer, deep oscillation resulted in significant relief of pain and subjective reduction of swelling [5].

This is the first prospective randomized and controlled study analysing the effect of deep oscillation and biofeedback training compared to a control group in patients with Raynaud's phenomenon secondary to SSc. Even with the low number of patients, we saw an improving effect of physiotherapy on RP compared to the control group suggesting a high impact of therapy. The effects of biofeedback on secondary RP seem to be higher compared to deep oscillation with more significant changes compared to the control group.

Our study confirmed the effect of biofeedback also suggested by retrospective studies of patients with secondary RP due to different diseases also in SSc patients in a randomized prospective controlled setting [6, 7]. However, despite a more severe and progressive disease in the intervention groups as exemplified by the longer disease duration and higher mRSS, differences in the alterations were still present underlying the significant effects of these physiotherapies.

Biofeedback appears to be a very good tool and might be used at home by educated patients. Compared to deep oscillation, this therapy requires less personal resources.

One limitation of the study is the use of a subjective symptom as primary outcome that cannot be validated by objective methods and is thus prone to be influenced by the wish of patients to be successfully treated. Nevertheless, deep oscillation with the potential of a higher placebo effect was not superior to biofeedback. Another limitation is the low number of patients. In collaboration with the Clinic for Rheumatology, as a centre of special interest in SSc, we were able to screen a high number of patients ($n = 220$), but only 28 could be included. Reasons were mostly a too far advanced disease but also the fact that most of the patients treated in such a centre, already participated in other clinical trials or got specific therapies that interfered with the studies' inclusion criteria. However, sample size in most other studies regarding biofeedback in RP is comparable [6–9].

In conclusion, as shown here by investigating both biofeedback and deep oscillation, physiotherapy provides a rational approach for the treatment of RP and should receive attention as therapy in SSc patients.

Acknowledgments The study was supported by grants from Physiomed Elektromedizin AG, Schnaittach/Laipersdorf, Germany. The authors disclose that the views of the funding body have not influenced the content of the paper.

Conflict of interest The authors disclose that there is no conflict of interest.

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