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Is Low-Level Laser Therapy an Effective Treatment for Patients with Primary Raynaud's Phenomenon?

Adriana S. Ruiz
Philadelphia College of Osteopathic Medicine, adrianaru@pcom.edu

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Adriana S. Ruiz, PA-S

A SELECTED EVIDENCE BASED MEDICINE REVIEW

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pa

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not low-level laser therapy is an effective treatment for patients with primary Raynaud's Phenomenon.
STUDY DESIGN: Review of three randomized, double blind, placebo controlled trials, published between 2002-2004.
DATA SOURCES: Randomized, double blind clinical trials comparing low-level laser therapy with a placebo treatment were found using the Cochrane databases, and PubMed.
OUTCOME MEASURED: Reduction in frequency and severity of Raynaud's attacks. Outcomes were measured and recorded with daily diaries of attacks before and after the intervention, and thermographic studies.
RESULTS: Three RCTs were included in this review. The RCT by Hirschl et al. 2002, showed a decrease in frequency of attacks from 0.86 to 0.67 with the laser therapy, which was more than with the sham treatment, but not statistically significant. It was, however, significant in lowering the intensity of attacks. The RCT by Hirschl et al. 2004 showed that both the number of attacks and their intensity were significantly reduced during the period of laser therapy compared to the sham treatment. Intensity of attacks was reduced 82% with laser therapy. The RCT by Al-Awami et al. 2004, also showed a statistically significant improvement in both frequency and intensity of attacks.
CONCLUSIONS: All three RCTs showed that low level laser therapy decreased the frequency or intensity of Raynaud's attacks more effectively than when exposed to a sham treatment, and it seems to be an option for treating these attacks. Further studies should be conducted to understand the pathogenetic mechanism of LLLT on Raynaud's phenomenon and it's place in treatment.

Key Words: primary Raynaud's phenomenon; low-level laser therapy

INTRODUCTION

Raynaud's is a disorder in which small blood vessels of the extremities have reduced blood flow when they are exposed to cold, or emotional distress. Under these conditions, the blood vessels go into spasms, causing pain, numbness, throbbing or tingling. Typically, the fingers are most commonly affected, changing from white and even blue within minutes of exposure, and then becoming red after being warmed. Primary Raynaud's is not linked to an underlying medical condition, whereas secondary Raynaud's is associated with another condition or disease, usually rheumatic in nature.[1] Although Raynaud's phenomenon is often self-limiting, vasodilator drugs have been used in severe cases where it interferes with the person's life. However, these drugs many times have restrictions; such as lack of consistency, tolerance development and side effects that may become intolerable for the patients.[2] This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of low-lever laser therapy (LLLT) with no treatment, with the ultimate goal of reduction in frequency and intensity of Raynaud's attacks.

Raynaud's attacks affect up to 10% of the adult population, hence making it relevant to all healthcare providers, including physician assistants in practice. It tends to target females more than males.[2] During a Raynaud's attack, the pallor of the digits, that cause cyanosis, pain and numbness, lead to a decreased quality of life, and restrict patients from performing certain activities or occupations.[2,3] The cost of this condition has not been determined due to the fact that only 1 in 5 people with this condition are aware that it is medically related and actively seek treatment.[1] The condition may be mild and not affecting their daily lives, and they may simply attribute it to having poor circulation or being sensitive to cold climates.[1] Many will often present to a primary care doctor and be referred to a rheumatologist.[1]

Primary Raynaud's phenomenon is often a benign disease, but it often reduces a patient's quality of life. The underlying pathogenic process in Raynaud's phenomenon is unclear.[2] Studies suggest the possibility of endothelial dysfunction. It has been shown that there are increased levels of endothelial function and platelet activation, including the release of endothelin and von-Willebrand factor. These factors reduce the endothelial release of nitric oxide, leading to the proposition that Raynaud's phenomenon could have to do with endothelial-dependent vasoregulation.[2]

Current methods used to treat this condition include self-limiting treatment, which is simply keeping warm, and putting extremities under warm water[2]. However, this is not treatment enough for many people. Biofeedback has also been tried with limited results.[4] Vasodilator drugs have been used with some success, including calcium channel blockers and α- adrenergic blockers. However, most of these drugs have side effects or limitations, including lack of consistency, development of tolerance, development of side effects including dizziness, headaches, palpitations, and orthostatic hypotension.[2] For this reason, low-level laser treatment is being proposed. The use of low-level laser therapy has been shown to improve patient's complaints in frequency and severity or attacks compared to placebo treatment without the side effects.[2]

OBJECTIVE

The objective of this selected EBM review is to determine whether or not low-level laser therapy is an effective treatment for patients with primary Raynaud's phenomenon.

METHODS

Criteria for selection of studies included patients with primary Raynaud's phenomenon. The intervention used was low-level laser therapy, and was compared with no

treatment, which in this case was a sham laser. The outcomes measured in these studies were the reduction in frequency and severity of Raynaud's attacks in patients with primary RP. The studies included in this EBM review include 3 RCTs comparing LLLT with no treatment.

Key words used in searches included: primary Raynaud's phenomenon and low-level laser therapy. Two articles were first published in German: M. Hirschl et al. Double-blind, randomized, placebo controlled low level laser therapy study; and M. Al-Alwami et al, Low Level laser therapy for treatment of RP. One article was published in English: Hirschl et al: Laser therapy in RP. All articles were published in peer-reviewed journals. Literature searches occurred via Cochrane databases and PubMed. Articles were selected based on importance of outcomes to the patient (POEMS). Inclusion criteria included patients with primary Raynaud's phenomenon (RP). The diagnosis of primary RP was established by the exclusion of associated disease or known cause for RP. Patients under the age of 18 were excluded, those over the age of 65, and those women of childbearing age not using adequate contraception. Also, patients could not be using any vasoactive medication. Summary of statistics reported or used were p-values, Wilcoxon paired test, ANOVA, Chi-square, Bartlett test, and the Kolmogorov-Smirnov test. Table 1 demonstrates the demographics included in the studies.

Table 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age yrs	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
M. Al-Awami, 2004 [2]	RCT	47	18-65	Patients with RP for 2 yrs or more and at least 4 episodes of RP per week. Established dx of RP, by exclusion of associated diseases that cause secondary RP.	Any patients taking vasodilator drugs. Patients under the age of 18, over the age of 65, and women of childbearing age not using adequate contraception.	0	10 sessions of low level laser distant irradiation treatment. Exposure time: 1000 sec per session, intensity: 400 mW, power density 2.2 mW per square cm applied to palms and fingers of both hands simultaneously
M. Hirschl, 2002 [3]	RCT	15	36-70	Patients with established primary RP	Patients must be part of a long-term study, selected during the cold season of Dec. 2000-March 2001, in which diagnostic procedures for detection of underlying diseases and follow-up control established, for exclusion of secondary RP Patients could not use vasoactive medications	3	3-week period of diode array (low level laser 200 mW, wavelength 625 nm) for 30-40 min, 5 times per week.
Hirschl, 2004 [4]	RCT	48	32-60	Patients diagnosed with primary RP according to diagnostic clinical criteria. Patients unassociated with other diseases.	Patients taking vasoactive medication that could interfere with vascular response	2	3 week period of diode laser (power 200 mW, wavelengths 685 nm) for 30-40 min, 5 times per week

OUTCOMES MEASURED

The outcomes measured included the reduction in frequency and severity of Raynaud's attacks. The outcomes were measured in all the studies with recorded daily diaries of attacks before and after the intervention. Thermographic studies were also performed before in the study by Al-Alwami. The thermographic study was done before the start of the trial and 6 weeks after the irradiation. A standardized cold-warm challenge test using computerized thermography of continuous temperature recordings was performed. The basal finger-tip skin temperatures was performed after being in room temperature for 20 min; after 1 min. warm challenge (immersion of gloved hand in water at 39° C), and after 1 min. cold challenge (immersion of gloved hand in water at 20° C).

RESULTS

The three randomized controlled trials in this review were all presented in continuous data. None of the data was dichotomous and could not be converted to dichotomous data.

Al. Alwami et al. 2004, presented all continuous data, used Chi-square to compare proportions, and considered p-value < 0.05 as statistically significant. Paired continuous variables were compared by Wilcoxon paired test. Overall, the frequency and severity of patients with RP was reduced with LLLT (frequency $p < 0.0001$, severity $p < 0.0001$), better than with placebo (frequency $p < 0.0001$, severity $p < 0.02$). In addition, there was a significant improvement in frequency and severity at 6 weeks (frequency $p = 0.007$, severity $p = 0.02$) and 3 months (frequency $p = 0.02$, severity $p = 0.04$), as shown in Table 2.

Table 2: Comparison of the frequency and severity of RP attacks before and after LLLT and placebo treatment (tx)

	LLLT group (n = 24)	**Placebo group (n= 23)**	**P-value**
Baseline			
Frequency of RP	7	7	0.8
Severity of RP	6	5	0.5
6 weeks after tx			
Frequency of RP	3	5	0.007
Severity of RP	1	4	0.02
3 months after tx			
Frequency of RP	3	6	0.02
Severity of RP	0	4	0.04
P-value			
Frequency of RP	< 0.0001	<0.0001	
Severity of RP	< 0.0001	0.02	

Improvement in thermographic response to cold challenge was only seen in patients treated with LLLT and not seen in patients treated with placebo, as can be seen in Table 3. There were no adverse effects or safety concerns in patients treated with LLLT.

Table 3: Temperatures of patients measured during cold challenge test, before and 6 weeks after LLLT and placebo

	LLLT group (n = 24) C°	**Placebo group (n = 23) C°**
Cold challenge test- baseline		
Temperature difference after 20 min recovery	-2.3 °	-2.5 °
Cold challenge test – 6 weeks		
Temperature difference after 20 min recovery	-0.6 °	-1.0 °
P-value	0.02	0.1

Hirschl et al. 2002, presents the frequency and severity of attacks statistically by using the Bartlett's tests and the Kolmogorov-Smirnov test. For all statistical comparisons, a p-value less than 0.05 was considered significant. Table 4 shows frequency of attacks of Raynaud's attacks during the 3 weeks of LLLT or placebo. Relative frequency of RP attacks was reduced from 0.86 in week 1, to 0.67 in week 3 of LLLT, compared to the placebo with 0.90 in week 1 to 0.72 in week 3.

Table 4: Relative frequency of attacks during the 3 weeks of LLLT or placebo therapy

	Week 1	Week 2	Week 3
Laser	0.86 +/- 0.93	0.69 +/- 0.46	0.67 +/- 0.42
Placebo	0.90 +/- 0.83	0.86 +/- 0.67	0.72 +/- 0.32

Even though the frequency of attacks did decrease with LLLT, it was not statistically significant ($p = 0.520$). Table 5 shows the average intensity for each week, which did decrease significantly. In spite of this, there was no residual effect of LLLT after the third week, when no treatment was implemented; hence the effects of the laser therapy may only be of short duration.

Table 5: Mean Intensity of symptoms measured on a 5-point scale before treatment and at end of weeks 1 -3 of laser and placebo therapy

	Pre-Treatment	Week 1	Week 2	Week 3
Laser	3.3	2.5	2.5	2.6
Placebo	3.3	3.0	3.0	3.2

Hirschl et al. 2004, uses ANOVA to compare laser and placebo conditions, controlling for sequence of conditions to assess for potential differences across experimental conditions. Normality was assessed by the Kolmogorov-Smirnov tests. Ambient temperature was statistically not different between sham and laser exposure (sham 3.2 +/- 3.6 C°; laser 3.0 +/- 3.9 C°). Table 6 shows the frequency and the severity of attacks were significantly reduced during the LLLT compared to the sham treatment. Intensity of attacks was reduced with placebo was only slightly reduced (96% of pre-treatment intensity), compared to the results with the laser therapy (82% of pre-treatment intensity). Table 6 also shows that exposure or evoking conditions (cold, wetness, etc.) did not differ between pre-treatment phase and laser and place therapy phase, which where each 3 weeks. Although all measures were favorable for LLLT, none of them reached statistical significance, as shown by Table 6.

Table 6: Mean of average number of exposures per day, attacks per day, intensity of attacks (5-point scale, minimal to severe; absolute and relative to week preceding treatment) for each week of laser and placebo treatment

			Laser			**Placebo**		
	Pre	1st	2nd	3rd	1st	2nd	3rd	P
Exposure	3.0	3.0	2.9	2.9	2.9	3.0	2.9	0.881
Attacks	2.5	1.8	1.6	1.6	2.1	2.2	2.0	0.001
Attacks relative to exposure	90	72	66	66	83	82	78	0.008
Intensity	3.2	2.5	2.3	2.3	2.9	2.8	2.8	< 0.001
Intensity relative to pre-treatment		87	80	78	96	96	94	< 0.001

DISCUSSION

The study by Al-Awami was a double-blind placebo controlled trial, which showed that LLLT resulted in more significant improvement in the symptoms of Raynaud's attacks, when compared with the placebo treatment. Even though there was an improvement in frequency and severity in RP attacks, there was also some improvement with the placebo treatment. This shows possible psychological influence. However, LLLT had a more significant improvement of patient complaints. There was also a thermographic improvement that the placebo treatment did not have. In terms of demographics, the diversity among patients with RP is a weakness in the trial, with patients ranging from 18-65 years old. There were no noted side effects during the trial with LLLT, making the efficacy of this laser treatment more appealing in the treatment of primary RP.

The study by Hirschl et al. 2002, demonstrates that ultimately the frequency of attacks is only slightly influenced by LLLT, and not statistically significant. However, severity of attacks is statistically significantly reduced. Despite the randomized crossover design of the trial, the psychological effect of patient expectations must be considered. Unfortunately, the slightly

positive effects of LLLT are only in short duration, and there was no transfer effect from laser to sham condition.

Finally the study by Hirschl et al. 2004, also using a crossover design, using each subject as their own control, showed that frequency and intensity of attacks was reduced by a clinically significant amount. The study demonstrated that patients with cold as the only trigger, and patients that have a more pronounced temperature decrease, showed a better response to LLLT. This may suggest an intrinsic heterogeneity of the clinical presentation of primary RP, and differential therapeutic effects based on the differing intensity of vasospasms after cold provocation. This could possibly be due to endothelium- independent factors, a current theory of the pathogenesis of RP that must be further studied. Even though there was a beneficial effect with placebo, the effects failed to reach statistical significance, while those treated with LLLT had a substantial therapeutic effect in this trial. Although LLLT seems promising, there may not be much more than scientific interest to overcome the shortage of available resources that would make this treatment clinically effective.

CONCLUSION

Based on the studies reviewed, low-level laser therapy appears to be an effective treatment in treating patients with primary Raynaud's phenomenon. Even though there were some improvements seen in the placebo groups as well, attributing some of the improvements to psychological effect, those subjects treated with LLLT had a more significant therapeutic effect in all of the trials. In addition, none of the studies showed side effects or undesirable outcomes, demonstrating that LLLT is a safe and effective alternative to the current treatments for those with primary Raynaud's phenomenon. The trials, however, showed the effects of LLLT to be of short-term benefit, and not necessarily a permanent or long duration treatment.

The underlying mechanism of action of LLLT is still unknown, and further studies should be implemented to determine this mechanism, whether it is due to endothelium-independent factors or not. Also providing more insight into the mechanism of action of LLLT may help in promoting endurance in the effects of this therapy. More knowledge in this area may help make this treatment one that is more desirable and help overcome the possible shortage of available resources that forms a barrier to making this an efficient and effective treatment for those patients with primary Raynaud's phenomenon.

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