Original article Effects of Low-Level Laser Therapy with Wrist Splinting on Outcome of Patients with Carpal Tunnel Syndrome; A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract:

Introduction: To determine the long-term effects of low-level laser therapy (LLLT) on clinical symptoms and electrophysiological parameters of patients with mild and moderate carpal tunnel syndrome (CTS).

Methods: This randomized, double-blind, placebo-controlled trial was conducted during a 1year period in January 2015 to January 2016 in outpatient clinics of Isfahan University of Medical Sciences. This study is registered with Iranian Clinical Trial Registry (IRCT20120716010297N5). We included 61 hands with mild and moderate CTS from both genders with an age range of 30 to 65 years. The hands were randomly assigned to receive LLLT and night wrist splint (n=31) or sham laser therapy and night wrist splint (n=30). Symptoms severity scores (SSS), functional severity score (FSS), visual analogue scale (VAS) and nerve conductive study (NCS) parameters using electrodiagnostic equipment were evaluated based on clinical parameters (Phalen's and Tinel tests) at 6 months after treatment.

Findings: The baseline characteristics were comparable between two study groups. The VAS, SSS, FSS, peak sensory latency and distal motor latency decreased significantly in both study group after 6 months of intervention. We found that those receiving LLLT had significantly lower VAS (p=0.001), SSS (p<0.001) and FSS (p<0.001) compared to sham laser therapy after 6 months of follow-up. In the same way, those in LLLT group had significantly lower values of peak sensory latency compared to sham group (p<0.001). Those receiving LLLT had significantly higher decrease in mean values of VAS (p=0.032), SSS (p=0.021), FSS (p=0.002) and distal motor latency (p<0.001) when compared to those in sham group. However, the decrease in mean differences of peak sensory latency was comparable between two study groups.

Conclusion: LLLT is associated with improved pain, symptoms, function and sensory evoked potentials after 6 months in patients with mild to moderate CTS.

Keywords: Low-Level Laser Therapy; Carpal Tunnel Syndrome (CTS); Wrist Splint; Outcome

Introduction:

Carpal tunnel syndrome (CTS) is the most common compression neuropathy associated with pain, throbbing and tingling of knuckles with an estimated general incidence of 0.125-1%, and prevalence of 5-16%, depending upon the criteria used for the diagnosis (1-3). The disease can cause mild, moderate and severe disabilities in the hand function resulting in weakness, paresthesia and muscle wastage (4). Early diagnosis and treatment of this syndrome leads to a significant reduction in symptoms and postponement of the irreversible complications (5). Several approaches have been introduced and tested for treatment of CTS. The conservative approaches such as localized steroid injections, ultrasound, electromagnetic therapy, night splinting and ergonomic keyboard have been shown to be associated with short-term recovery of the symptoms with different results (6, 7). However, the medium-term and long-term effects of these interventions has not been well established (8). The wrist splints are conservative most frequently used treatment for the patients with CTS with the mechanism of minimizing the median nerve compression by providing appropriate wrist position. The splinting efficiency in non-severe carpal tunnel syndrome is about 60 to 70% (9, 10).

Low-level laser therapy (LLLT) has been extensively used for treatment of several musculoskeletal disorders including the CTS despite appropriate clinical evidence (11-13). However, in recent years, several clinical trials have tested the efficacy and safety of the LLLT on short-term outcome of patients with CTS (14-17). Some of these trials have demonstrated that LLLT is associated with improved clinical and electrophysiological parameters especially when used in early stages of the disease (14, 15), while some others found no additive effect of LLLT compared to sham laser therapy for treatment of patients with CTS (16, 17). In the same way, several recent systematic review and metaanalysis tested the hypothesis that LLT is associated with improved functional and electrophysiological outcome parameters. All of these studies reported lack of appropriate evidence for analysis and reported that more high-quality studies are needed to confirm the effects of LLLT in the treatment of CTS (18, 19). In addition, it was reported that longer follow-up periods are required to establish the efficacy of LLLT for CTS treatment while most of the available trials have determine the short-term outcome (11, 12). Thus. we conducted the current randomized, placebo controlled clinical trial in order to determine the effects of LLLT on the long-term clinical and electrophysiological outcome of patients with mild to moderate CTS.

Methods:

Study population:

This randomized, double-blind, placebocontrolled trial was conducted in several outpatient physical medicine and rehabilitation clinics of Isfahan University of Medical Sciences during a 1-year period from January 2015 to January 2016. We included a total those hand with mild to moderate CTS aging between 30 to 65 years referred to these centers during the study period. The CTS was diagnosed according the clinical to and electrophysiological findings. All the hands had pain and numbness in the median nerve territory, positive Phalen's

and Tinel test and mild or moderate involvement of median nerve at the wrist according to electrophysiological findings. The mild CTS was defined as prolonged sensory latency of median nerve from the middle finger, >3.6 mSec; while the moderate CTS was defined as prolonged sensory latency of median nerve from middle finger, \geq 3.6 mSec prolonged motor latency of the median nerve >4.2 msec. We excluded the hands with severe CTS based on electrodiagnostic criteria defined as prolonged median motor and sensory distal latencies, with either an absent sensory nerve action potential (SNAP) or compound nerve action potential (CNAP), or low-amplitude or absent thenar compound muscle action potential (CMAP). We also excluded those receiving analgesic or anti-inflammatory drugs, those previously treated with LLLT, history of steroid injection for CTS, those with history of thyroid disease, diabetes or peripheral neuropathy, anatomic abnormalities caused by trauma and wrist fracture and those with history of rheumatic or metabolic diseases. The study protocol was approved by the institutional review board (IRB) and the medical ethics committee of Isfahan University of Medical Sciences. The study protocol is also registered by the Iranian registry for clinical trials (IRCT20120716010297N5). All the patients provided their informed written consents before inclusion in the study.

Randomization and Intervention:

All the hands were randomly assigned to two intervention group using a computerbased random digit generator based on the consecutive admission numbers. Those who were assigned to the LLLT group received LLLT for 10 sessions (three times a week) using the calibrated laser device

model 620 laser med with continuous wave at 880 nm and a pulse wave of 905 nm with a maximum power output of 1100 mV and frequency of 1000 Hz. The duration of each session was 20 minutes with the protocol of 500 mW, 880 nm, 6 joules per square centimeter at any point, at 10 points in the volar wrist in the carpal tunnel within 1-cm intervals on а rectangular Those zone. who were assigned to the sham laser therapy group received the same instruction with the laser device being turned off. In both groups, vitamin B1 at a dose of 300 mg per day and static night splinting for wrist was administered for two months. All the subjects were taught how to correctly use the wrist splint.

Follow-up and Outcome Measures:

All the hands were followed for 6 months after the intervention and were visited in outpatient clinics. hands The were evaluated both clinically and electrophysiologically. We measured the pain intensity using the visual analog scale (VAS) while other symptoms were evaluated using the symptom severity scale (SSS). The functional outcome of the hands was assessed using the functional status scale (FSS). We also checked the Phalen and Tinel tests in 6-month followup visit. The electrophysiologic study was also performed for all the hands in 6month visit. The nerve conductive parameters included peak sensory latency and distal motor latency. All the clinical examinations and the electrophysiological studies were performed by a physician who was blinded toward the study groups. The hands were also blinded toward their study group. Only the statisticians were aware of the study groups.

Statistical Analysis:

The sample size was calculated to be 70 subjects at confidence level of 95% and 80% power factor based on the following equation:

$$n = \frac{2(z_1 + z_2)^2 s^2}{d^2}$$

 Z_1 is 1.96 confidence or 95%.

 Z_2 is power factor of 80% or 0.84.

S is an estimate of standard deviation of each variable in the two groups, d is the minimum average difference between the two groups, indicating any significant difference at S=0.10.

All the statistical analyses were performed using the statistical package for social sciences (SPSS Inc., Chicago. Illinois, USA). All the data are presented as mean \pm SD and proportions as appropriate. In order to compare the parametric variables with normal distribution between the two study groups we used the independent ttest and Mann-Whitney U-test was used to compare the parametric variables without normal distribution between the two study groups. Parametric variables with normal distribution were compared within groups using the paired t-test. Proportions were compared using the chi-square test. A 2sided p-value of less than 0.05 was considered statistically significant.

Findings:

Overall we evaluated 81 hands for eligibility out of whom 8 hands were not eligible and 3 refused to be included. Thus a total number of 70 hands were randomized into two study group (each including 35 hands). During follow-up period 9 hands were lost, 4 in LLLT group (two hands did not follow study treatment regimen and two hands did not desire to continue), and 5 in sham group (1 hand did not desire to continue, 3 hands did not follow study treatment regimen and 1 hand immigrated). Thus the final number of hands being included in the final analysis was 31 in LLLT group and 30 in sham group (Fig. 1). The baseline characteristics of the hands was comparable between the two study groups (Table 1).

In LLLT group the positivity of Tinel test decreased significantly after 6 months of follow-up (p=0.006). in the same was the positivity of the Phalen test decreased significantly after the follow-up period (p=0.004). After 6 months of follow-up, we found that those receiving LLLT had lower rates of Tinel (p=0.016) and Phalen (p=0.012) tests positivity when compared to the sham laser group (Table 2). The VAS, SSS, FSS, peak sensory latency and distal motor latency decreased significantly in both study group after 6 months of intervention (Table 3). We found that those receiving LLLT had significantly lower VAS (p=0.001), SSS (p<0.001) and FSS (p<0.001) compared to sham laser therapy after 6 months of follow-up. In the same way, those in LLLT group had significantly lower values of peak sensory latency compared to sham group (p<0.001). However, distal motor latency was comparable between the two study group (p=0.123). Table 4 compares the decreased in mean values of outcome measures after 6 months of therapy study between two groups. As demonstrated, those receiving LLLT had significantly higher decrease in mean values of VAS (p=0.032), SSS (p=0.021), FSS (p=0.002) and distal motor latency (p<0.001) when compared to those in sham group. However, the decrease in mean differences of peak sensory latency was comparable between two study groups.

Discussion:

The effects of LLLT on pain and functional outcome of patients with CTS has been previously studied extensively (11, 12, 14, 18). However, there is still controversy regarding the outcome and lack of appropriate long-term evidence leads to uncertain results of systematic reviews and the meta-analysis. In this randomized, placebo-controlled clinical trial we tried to investigate the effects of LLLT on long-term outcome of patients with mild to moderate CTS. We found that LLLT was associated with decreased pain intensity and improved symptoms along with improved functional outcome after 6 months. We also found that LLLT resulted in improved sensory evoked potentials without any effect on the motor evoked all potentials. Taking these results together, it could be concluded that LLLT might be an effective and safe conservative modality for treatment of patients with mild to moderate CTS.

Several studies have evaluated the LLLT on outcome of patients with CTS have showed beneficial effects with different follow-up durations (15-17, 20). Lazovic et al. demonstrated significant (15)pain, reduction in the reduction in percentage of patients with a positive Tinel's sign, and shortening of sensory and the NCS motor latency time in examination. These outcomes were recorded in short-term (3 weeks) and longterm results were not available (15). In another study, Irvine et al. (16)demonstrated no significant difference in any of the outcome measures between the LLLT and the sham laser therapy group. Dincer et al. (20) also demonstrated that LLLT plus splinting was more advantageous than ultrasonography

therapy plus splinting, especially for the outcomes of lessening of symptom severity, pain alleviation, and increased patient satisfaction. We demonstrated that LLLT was more effective than sham laser therapy in improving the clinical symptoms and functional outcome (VAS, FSS) SSS, and as well as electrophysiological parameters (peak sensory latency) 6 months after the treatment. This is among the few available studies in the literature addressing the long-term outcome of LLLT in patients with mild and moderate CTS.

There are several theories regarding the effects of laser on pain and inflammation control. The effect of low energy laser is not thermal, rather, it is believed to stimulate microcirculation and endorphin secretion, also block the enzymes that block pain enzymes leading to reduce pain and inflammation (21). In a study by Rayegani et al. (21) all patients in the three groups including LLLT study and splinting (A), sham LLLT+ splinting (B) and only splints (C) showed significant improvement regarding clinical symptoms (VAS, FSS, SSS) and Tinel and Phalen tests; however, comparison of the three groups in terms of clinical symptoms (VAS, FSS, SSS), Tinel and Phalen tests two months after the intervention was not significantly different. Most of the therapeutic effects of laser on clinical symptoms were noticed immediately after therapy. Electrophysiologic parameters improved 3 weeks after treatment and this improvement remained significant at follow-up (21). These findings are in concordance with our study although the follow-up duration has been less than ours. Raeissadat et al. (22) compared the longterm outcome of patients with CTS undergoing LLLT versus corticosteroid injection. They reported comparable results after 10 months of follow up (22). In another placebo-controlled study, Evcik et al. (23) randomly assigned 81 patients with CTS to receive LLLT or placebo laser. Although the results showed similar statistically significant improvements in both groups; however, hand grip, sensory, and motor distal latencies were found to have been improved only in the LLLT group (23). Tascioglu et al. (17) conducted a placebo-controlled and double-blind study to compare the outcome of patients with mild to moderate CTS treated with active laser with a dosage of 1.2 J/per painful point, active laser with a dosage of 0.6 J/per painful point, and placebo groups. They found that pain intensity, grip strength, SSS, FSS and nerve conduction studies improved significantly in all groups. There was no significant difference in any of the outcome measures among the groups (17).

We note some limitation to our study. First, we included a limited number of hands in the current study which might affect the outcome negatively. We assumed to include 32 hands in each study group to have 80% power for detection of 5% difference in main study outcomes. However, several hands were lost to follow because of long-term study period. Overall the number of included hands in each study group was less than calculated value. The final power of the study was calculated to be about 80% which is acceptable but further studies with larger study population is required. The second limitation wad that we did not compare the effects of different laser protocols and dosages. As demonstrated before, different dosages and protocols might affect the outcome (24, 25). Our proposed protocol LLLT for based on the was

recommendations by the World Association for Laser Therapy (WALT) for treatment of musculoskeletal disorders. Taking all these together, this is among the few available studies on long-term effects of LLLT on clinical symptoms and functional outcome of patients with mild to moderate CTS.

In conclusion, the results of current placebo-controlled randomized, study demonstrate that LLLT is associated with improved clinical symptoms measured by VAS. SSS and FSS and electrophysiological parameters (improved peak sensory latency) after 6 months in patients with mild to moderate CTS. Thus, LLLT might be effective in long-term for treatment of these patients. Further complementary studies are recommended.

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Conflict of Interest:

There isn't any conflict of interest to be declared regarding the manuscript.

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Tables:

Table I: Comparison of baseline characteristics between groups

		LLLT group (n=31)	Sham group (n=30)	P-value	
Age		46.9 ± 10.3	48.2 ± 8.8	0.59*	
Sex	Men (%)	11 (35.5%)	12 (40%)	0.72+	
	Women (%)	20 (64.5%)	18 (60%)	0.72	
Carpal tunnel	Mild (%)	16 (51.6%)	14 (46.7%)	0.69†	
syndrome status	Moderate (%)	15 (48.4%)	16 (53.3%)		
Duration of symptoms		13.5 ± 4.7	14.3 ± 3.6	0.48*	
Side of involvement	Right (%)	19 (61.3%)	15 (50%)	0.37†	
	Left (%)	12 (38.7%)	15 (50%)		
P-values calculated using *Independent sample t-test and †Chi square test					

Table 2: Comparison of Phalen and Tinel tests between studied groups

	Group	Baseline	After 6 month	P-value	
Tinel test (+)	LLLT (n=31)	18 (58.1%)	4 (12.9%)	0.006	
	Sham (n=30)	19 (63.3%)	12 (40%)	0.15	
	P-value	0.67	0.016		
Phalen test (+)	LLLT (n=31)	17 (54.8%)	3 (9.7%)	0.004	
	Sham (n=30)	12 (40%)	11 (36.7%)	0.92	
	P-value	0.24	0.012		
P-values calculated using Chi square test					

Table 3: Comparison of studied variables at time points between groups

	Group	Baseline	After 6 month	P-value ¹	P-value ³	P-value ⁴
Visual analogue scale	LLLT (n=31)	5.5 ± 2.2	2.3 ± 1.4	< 0.0001	0.040	0.016
	Sham (n=30)	5.9 ± 1.9	3.7 ± 1.6	< 0.0001	0.049	0.016
	P-value ²	0.55	0.001			
Symptoms severity score	LLLT (n=31)	29.3 ± 9	20.9 ± 6.2	< 0.0001	0.002	0.07
	Sham (n=30)	31.6 ± 6.4	27.8 ± 5.3	< 0.0001	0.002	
	P-value ²	0.25	< 0.0001			
Functional Severity Score	LLLT (n=31)	24.6 ± 6.1	16.5 ± 4.7	< 0.0001	0.02	0.005
	Sham (n=30)	25.4 ± 4.9	21 ± 3.4	0.023	0.02	
	P-value ²	0.58	< 0.0001			
Peak Sensory Latency	LLLT (n=31)	4.3 ± 0.59	3.4 ± 0.35	< 0.0001	0.042	0.01
	Sham (n=30)	4.4 ± 0.58	3.7 ± 0.42	0.002	0.042	
	P-value ²	0.6	0.001			
Distal Motor Latency	LLLT (n=31)	2.8 ± 2.2	2.1 ± 1.6	< 0.0001	0.34	0.003
	Sham (n=30)	3.1 ± 2.1	2.8 ± 1.8	< 0.0001	0.54	
	P-value ²	0.71	0.1			

P¹, assessed variables within groups in month-6 compare to baseline and was calculated by Paired sample t-test.

 \mathbf{P}^2 , assessed variables between groups at each time point and was calculated by Independent sample t-test.

P³, assessed trend of variables between groups by repeated measurements of ANOVA.

 \mathbf{P}^4 , assessed variables between groups by ANCOVA for month-6 after controlling baseline values as covariate.

Table 4: Mean differences of studied van	riables after intervention	compare to baseline between groups
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	LLLT group (n=31)	Sham group (n=30)	P-value		
Visual analogue scale	-3.2 ± 2	-2.2 ± 1.5	0.032		
Symptoms severity score	-8.4 ± 8.9	-3.8 ± 5.9	0.021		
Functional Severity Score	-8.1 ± 5.5	-4.3 ± 3.1	0.002		
Peak Sensory Latency	-0.84 ± 0.53	-0.62 ± 0.5	0.110		
Distal Motor Latency	-0.83 ±0.72	-0.3 ± 0.27	< 0.0001		
Data are mean ± SD.					
P-values calculated using Independent sample t-test.					

