Arch Rheumatol 2022;37(1):19-30
doi: 10.46497/ArchRheumatol.2022.8605

ORIGINAL ARTICLE

Ultrasonographic and electrophysiological outcomes of carpal tunnel syndrome treated with low-level laser therapy: A double-blind, prospective, randomized, sham-controlled study

Merve Nalbant[1], Oya Ümit Yemişci[2], Selin Özen[2], Şehnaz Tezcan[3]

[1]*Department of Rheumatology, Mersin University Faculty of Medicine, Mersin, Turkey*
[2]*Department of Physical Medicine and Rehabilitation, Başkent University Faculty of Medicine, Ankara, Turkey*
[3]*Department of Radiology, Koru Hospital, Ankara, Turkey*

ABSTRACT

Objectives: The aim of this study was to investigate the therapeutic effects of low-level laser therapy (LLLT) on clinical, ultrasonographic (US), and electrophysiological findings in carpal tunnel syndrome (CTS).

Patients and methods: Between January 2015 and August 2015, 42 patients (7 males, 35 females; mean age: 50.4±8.7 years; range, 32 to 65 years) with mild-to-moderate CTS were randomly assigned to one of two groups: active LLLT (therapy group, n=22) 0.8 J/painful point and sham LLLT groups (n=20). Both groups wore neutral wrist orthoses. The patients were evaluated before and after 15 sessions of therapy (670 nm, 4 J/session over the carpal tunnel). Follow-up parameters included the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) Symptom Severity Scale (SSS), Functional Status Scale (FSS), nerve conduction studies and US evaluation of the median nerve cross-sectional area (CSA), vascularization (via power Doppler), flattening ratio (FR), and palmar bowing of the flexor retinaculum.

Results: Nocturnal paresthesia improved in both groups; however, pain and patients with a positive Phalen's test reduced only in the therapy group (p=0.031). The FSS and SSS scores also improved only in the therapy group (p<0.001). Electrophysiologically, median sensory nerve conduction velocities showed a significant improvement only in the therapy group (p=0.002). The CSA, FR, and vascularization of the median nerve showed a significant improvement in the therapy group alone (p<0.001, p=0.048, and p=0.021, respectively).

Conclusion: Improvements in the signs and symptoms of CTS and hand function, the improvements in sensory nerve conduction studies, and reduction in median nerve CSA, FR and vascularity in the LLLT group can be attributed to the anti-inflammatory and analgesic effects of LLLT. This study provides new US data demonstrating efficacy of LLLT along with a clinical and electrophysiological improvement. The LLLT seems to be an easily applied, non-invasive treatment option.

Keywords: Carpal tunnel syndrome, diagnostic ultrasonography, electrophysiology, low-level laser therapy.

Carpal tunnel syndrome (CTS) is the most commonly seen entrapment mononeuropathy with a prevalence of 1 to 5%. It can be defined as the compression of the median nerve at the level of the carpal tunnel (CT) of the wrist, largely resulting in sensory symptoms such as paresthesia and pain in the hand.[1] Carpal tunnel syndrome can also lead to muscle atrophy, loss of motor function, and disability of the hand. Although the pathophysiology of CTS has not fully understood yet, it most likely includes mechanical damage to the median nerve with build-up of pressure in the CT resulting in nerve ischemia which, in turn, leads to fibrosis, axonal loss and demyelination.[2]

Received: November 26, 2020 ***Accepted:*** April 30, 2021 ***Published online:*** October 13, 2021

Correspondence: Oya Ümit Yemişci, MD. Başkent Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, 06490 Bahçelievler, Ankara, Türkiye.
Tel: +90 555 - 295 48 98 e-mail: oyaumit@hotmail.com

Citation:
Nalbant M, Ümit Yemişci O, Özen S, Tezcan Ş. Ultrasonographic and electrophysiological outcomes of carpal tunnel syndrome treated with low-level laser therapy: A double-blind, prospective, randomized, sham-controlled study. Arch Rheumatol 2022;37(1):19-30.

Diagnosis of CTS is made based on clinical symptoms and physical examination findings and confirmed using electrodiagnostic studies. In recent years, diagnostic ultrasound (US) has proven to be a valuable additional tool in the assessment of CTS.[3] The US imaging of median nerve flattening ratio (FR), vascularity, cross-sectional area (CSA), and soft tissue strain have proven to be of value in the diagnosis and prognosis of CTS.[4-6] Palmar bowing of the flexor retinaculum (PBFR) can be used as a measure of the internal pressure exerted on the retinaculum from the structures within the CT to help predict a diagnosis of CTS.[7] Ultrasound is not only used to analyze the morphology of the median nerve, but also to exclude the presence of anatomic variants and space-occupying lesions, such as ganglion cysts.

Physical therapy (PT) modalities such as laser are included in the conventional, non-surgical treatment of mild-to-moderate CTS.[8] Several studies have reported that low-level laser therapy (LLLT) can effectively treat mild-to-moderate CTS, resulting in an improvement in hand grip strength and electroneurophysiological parameters compared to placebo and use of wrist orthotics alone.[9-13] It is considered that the therapeutic benefits of LLLT may be due to its ability to increase myelin production, selectively inhibit nociceptor activity at the level of the peripheral nerves, improve blood circulation, and have anti-inflammatory properties.[14-17] On the contrary, there are also studies disproving the symptomatic benefits of LLLT in the treatment of CTS.[10,18,19]

To date, there is only one study evaluating the clinical, electrophysiological, and US outcomes of the treatment of CTS using LLLT. However, this study only includes cross-sectional area measurements of the median nerve using US.[12] In the present study, we aimed to investigate the therapeutic effects of LLLT on clinical, US, and electrophysiological findings in CTS including median nerve CSA, FR, PBFR, and vascularization by using power Doppler US.[20]

PATIENTS AND METHODS

This double-blind, prospective, randomized, sham-controlled study was carried out at Başkent University Faculty of Medicine, Department of Physical Medicine and Rehabilitation (PMR) between January 2015 and August 2015. Patients over the age of 18 presenting to the PMR outpatient clinic with a diagnosis of idiopathic CTS were screened. The diagnosis of CTS was confirmed using clinical and electrophysiological tests. Patients with electroneuromyographic (ENMG) findings of mild-to-moderate CTS in accordance with the guidelines of the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) were included in the study.[21] The most symptomatic hand of those diagnosed with bilateral CTS was included in the study. In patients in which both hands were equally symptomatic, the hand with more severe electrophysiological findings was included in the study. Exclusion criteria were as follows: *(i)* a diagnosis of cervical radiculopathy, polyneuropathy, brachial plexopathy, a proximal median nerve neuropathy, an ulnar nerve compression neuropathy, pathology affecting the neuromuscular junction, fibromyalgia syndrome; *(ii)* a diagnosis of inflammatory diseases such as rheumatoid arthritis and hypothyroidism; *(iii)* lymphoedema of the index upper extremity, wrist fracture, malignancy, diabetes mellitus, chronic liver or kidney failure; *(iv)* Steroid injection/PT to the index wrist as treatment for CTS over the past three months or previous surgical management of CTS; *(v)* those in which electrodiagnostic testing was contraindicated; those with a cardiac pacemaker, coagulopathy, or those taking anticoagulants; and *(vi)* Pregnancy. Finally, 42 patients (7 males, 35 females; mean age: 50.4±8.7 years; range, 32 to 65 years) with mild-to-moderate CTS were included. The study flow chart is shown in Figure 1. A written informed consent was obtained from each participant. The study protocol was approved by the Başkent University Faculty of Medicine Ethics Committee (KA15/159). The study was conducted in accordance with principles of the Declaration of Helsinki.

Randomization

The patients were randomized into one of two groups: LLLT (therapy group) and sham LLLT (control group) groups using opaque closed envelopes each containing either the number one

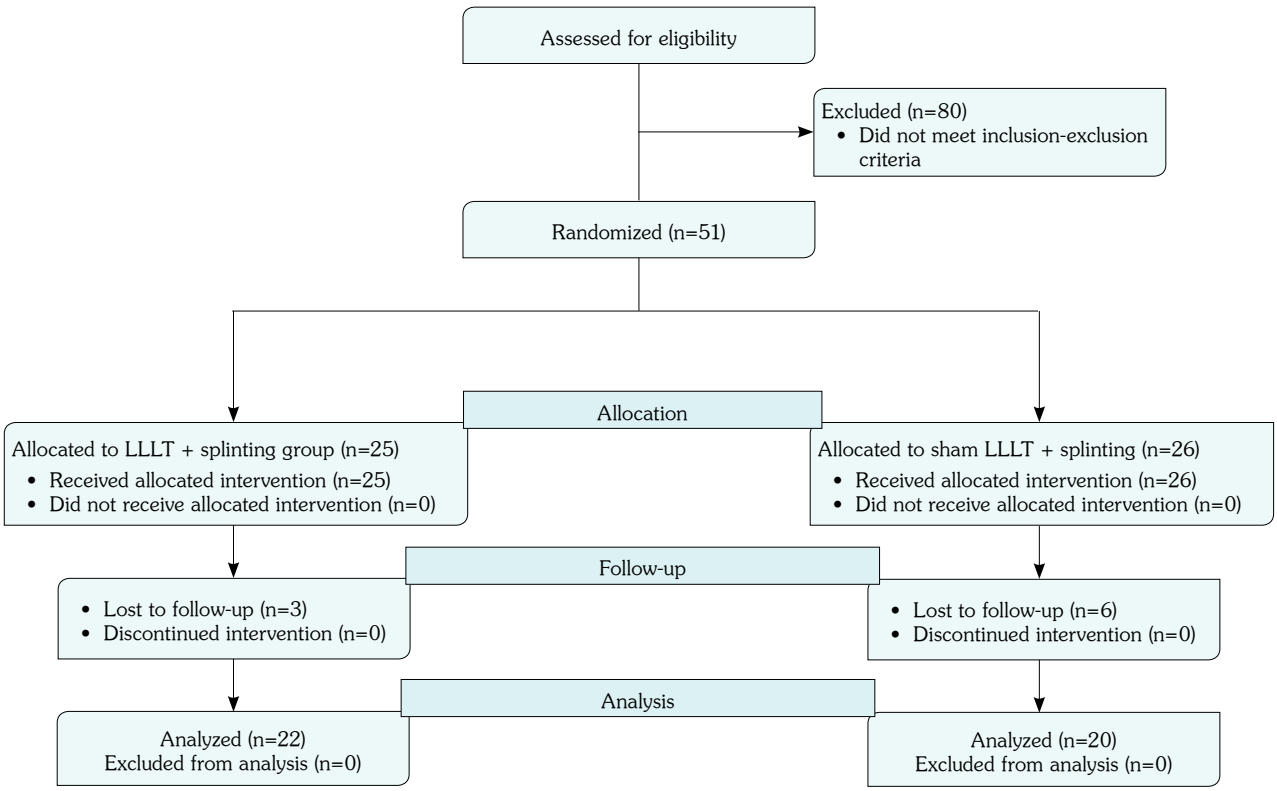

Figure 1. Study flow chart.

or number two. The randomization was carried out by an individual who was not involved in the conduct of the study.

Clinical assessment

All patients underwent clinical assessment by a single physiatrist blinded to the treatment group before treatment and during the first week after treatment. The demographic characteristics and body mass index (BMI) of all patients were recorded. Physical examination included joint range of motion and neurological examination of the upper extremities. Special tests included the Tinel's sign, Phalen's and reverse Phalen's test. Symptom severity and function was determined using the Turkish version of the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ);[22] the validity and reliability of the Turkish version of the BCTQ has previously been shown.[23] The Symptom Severity Scale (SSS) of the BCTQ includes 11 questions, the Functional Status Scale (FSS) of the BCTQ is comprised of eight questions. The answers for each question are graded from one to five, and the average of all the questions answered provides the final score. A higher score indicates worse symptoms and greater disability.

Electrophysiological assessment

Electrophysiological assessment of all patients was performed prior to and in the week following completion of treatment. Electrophysiological studies were conducted using a Medelec® Synergy Multimedia electrodiagnostic device (Oxford Instruments, UK) by a single physiatrist who was blinded to patients' treatments and assessments. All electrophysiological studies were performed at a minimum ambient temperature of 25°C and extremity temperature above 32°C. Median and ulnar nerve motor conduction velocities (MCV) (m/sec), compound muscle action potential (CMAP) amplitudes, and distal motor latencies (DML) were measured. Median and ulnar nerve sensory conduction velocities (SCV), sensory nerve action potential (SNAP) amplitudes, and distal sensory latencies (DSL) were recorded using ring electrodes placed on the third

and fifth fingers antidromically. Furthermore, median nerve mixed SCV and SNAP amplitudes of forearm and palm-wrist were evaluated.

The radial and lower extremity nerve conduction studies were conducted to rule out polyneuropathy. Needle electromyography (EMG) of the abductor pollicis brevis was conducted in patients with median motor nerve conduction abnormalities, if needed, and to exclude radiculopathy. Electrophysiological parameters were assessed according to the reference values determined by our laboratory.

US assessment

Diagnostic US imaging was performed by a single radiologist specializing in musculoskeletal and neuroultrasound, who was blind to the diagnosis of the patient, the treatment received and other assessment outcomes, before and in the first week following treatment. The scanner used in the study was an Acuson 3000™ (Siemens AG, Erlangen, Germany) with a 9.4 MHz linear array transducer. The patient was seated opposite to the sonographer and the fingers and elbow were flexed and the wrist supinated. Once the transducer was positioned on the volar surface of the wrist, longitudinal and transverse images of the median nerve along its entire course were obtained. The images were obtained from the proximal inlet of the CT at the level of the pisiform and the median nerve CSA was measured. The FR of the median nerve was calculated by dividing the length of its long axis by that of its short axis at the level of the pisiform (Figure 2).[24,25] Palmar bowing was determined by measuring the height from the deep margin of the flexor retinaculum perpendicular to a tangential line drawn between the most volar aspect of the trapezium and hook of hamate at the CT outlet (Figure 3).[26]

Median nerve vascularity was evaluated in the transverse plane using power Doppler. Standardized power Doppler settings were used (frequency 11.9 MHz, pulse repetition frequency 600 Hz) and vascularity graded from 0 to 3. Zero indicates no power Doppler signal, 1 indicates the presence of a single blood vessel, 2 indicates the presence of 2-3 vessels or two adjoining vessels, and 3 indicates the presence of three or more blood vessels and more than two adjoining vessels.[27]

Interventions

The therapy group received 15 sessions of LLLT, while the control group underwent 15 sessions of sham LLLT over a three-week period. All patients in both groups wore neutral wrist orthotics for 8 h per night[28] and were not allowed to receive any other medical treatment or PT for the treatment of CTS throughout the study. All participants were treated by a single physiotherapist.

The LLLT was administered using a Ga-Al-As infrared low-intensity diode laser device (Encre Intelect® Laser; Hixon Manufacturing and Supply Co., CO, USA) with a power output of 10 Mw and wavelength of 670 nm. The LLLT was administered with the probe held perpendicularly directly over the CT at five separate points (0.8 J/per point), administering 4 J of energy over the wrist for 2 min to a total of 60 J at the end of 15 sessions. Sham laser was administered

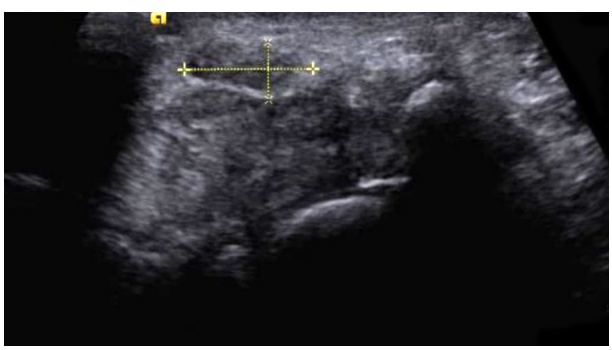

Figure 2. Ultrasound imaging of long and short axis of median nerve at the level of the pisiform.

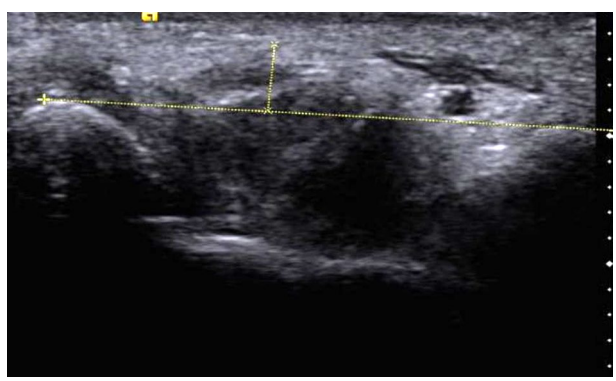

Figure 3. Ultrasound imaging of palmar bowing.

Table 1. Demographic and clinical characteristics of study population

	All patients (n=42)					Sham LLLT group (n=20)					LLLT group (n=22)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Mean age (year)			50.4±8.7					51.3±7.7					50.0±9.0			0.736*
Sex																0.982†¶
Male	7	16.7				3	15.0				4	18.2				
Female	35	83.3				17	85.0				18	81.8				
BMI (kg/m^2)			29.8±4.5					29.2±4.4					30.2±4.7			0.481*
Affected hand																0.996†
Right	23	54.8				11	55.0				12	54.5				
Left	19	45.2				9	45.0				10	45.5				
Dominant hand																0.982†¶
Right	35	83.3				17	85.0				18	81.8				
Left	7	16.7				3	15.0				4	18.2				
CTS symptom duration (month)				6	3-11				6.5	3-11				6	3-10	0.839‡
Occupation requiring repetitive hand movements																
Yes	27	64.3				13	65.0				14	63.6				0.927†
CTS severity																0.730†¶
Mild	31	73.8				14	70.0				17	77.3				
Moderate	11	26.2				6	30.0				5	22.7				

LLLT: Low-level laser therapy; SD: Standard deviation; BMI: Body mass index; CTS: Carpal tunnel syndrome; * Independent samples t-test; † Chi-square test (¶Fisher's exact test); ‡ Mann-Whitney U test.

Table 2. Comparison of clinical tests and parameters before and after treatment

	Sham LLLT group (n=20)							LLLT group (n=22)							
	Pretreatment			Posttreatment				Pretreatment			Posttreatment				
	n	%	Mean±SD	n	%	Mean±SD	p^{ab}	n	%	Mean±SD	n	%	Mean±SD	p^{ab}	p^{a}
Night time paresthesia	19	95.0		13	65.0		0.031**	20	90.9		12	54.5		0.008**	0.491*
Day time paresthesia	9	45.0		6	30.0		0.250**	8	36.4		4	18.2		0.219**	0.369*
Pain	14	70.0		12	60.0		0.500**	15	68.2		9	40.9		0.031**	0.217*
Positive Phalen's test	19	95.0		16	80.0		0.250**	11	50.0		5	22.7		0.031**	<0.001*
Positive Tinel's sign	9	45.0		7	35.0		0.625**	22	100.0		18	81.8		0.125**	0.881*
Positive reverse Phalen's test	6	30.0		5	25.0		1.000**	5	22.7		3	13.6		0.500**	0.349*
SSS			2.3±0.5			2.3±0.6	0.947***			2.5±0.4			2.0±0.4	<0.001†	0.144‡
FSSS			2.2±0.7			2.3±0.7	0.500***			2.4±0.6			2.0±0.6	<0.001†	0.225‡

LLLT: Low-level laser therapy; SD: Standard deviation; SSS: Symptom Severity Scale; FSS: Functional Status Scale; * Chi-square test ([a]: Comparison of post-treatment values between groups); ** McNemar test ([ab]: Comparison of pre- and posttreatment values per group); † Paired samples t-test; ‡ Independent samples t-test; [a]: Sham versus therapy group.

Table 3. Median nerve conduction parameters in all groups before and after treatment

	Sham LLLT group (n=20)							LLLT group (n=22)							
	Pretreatment			Posttreatment				Pretreatment			Posttreatment				
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	p^{ab}	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	p^{ab}	p^{a}
DML (ms)	3.7±0.5			3.8±0.5			0.569*	3.8±0.5			3.7±0.3			0.164*	0.520**
MCV (cm/s)	55.3±2.4			55.9±4.0			0.433*	56.2±2.6			55. 5±3.0			0.386*	0.120**
CMAP (μV)	7.6±1.9			7.7±2.3			0.496*	8.0±2.5			8.7±2.4			0.191*	0.182**
SCV (palm-wrist) (cm/s)	32.7±2.6			32.5±3.6			0.970***	31.3±3.3			33.3±3.4			0.008†	0.319‡
SNAP (palm-wrist) (μV)	28±14.2			33.2±12.6			<0.001***	37.9±17.9			42.9±22.6			<0.001†	0.134‡
SCV (forearm) (cm/s)	54.7±2.7			55.2±3.0			0.478***	53.7±2.8			54.3±2.7			0.426†	0.473‡
SNAP (forearm)		16	6.5-37.7		16.6	3.6-48.8	0.841***		15.1	8.8-84.3		15.6	5.7-63.1	0.876†	0.588‡
DSL (3rd digit-wrist) (ms)	3.8±0.5			3.7±0.6			0.819*	3.7±0.4			3.6±0.3			0.078*	0.093**
SCV (3rd digit-wrist)	32.1±3.5			32.3±3.7			0.711*	32.5±3.0			34.0±2.1			0.030*	0.071**
SNAP (3rd digit-wrist)		31.1	9.2-62.8		38.7	22.9-67.2	0.247***		31.1	5.3-98.0		39.6	16.1-90.8	0.339†	0.545‡

LLLT: Low-level laser therapy; SD: Standard deviation; DML: Distal motor latency; MCV: Motor conduction velocity; CMAP: Compound motor action potential amplitude; SCV: Sensory conduction velocity; SNAP: Sensory nerve action potential amplitude; DSL: Distal sensory latency; * Paired samples t-test; ** Independent samples t-test; † Wilcoxon signed-rank test; ‡ Mann-Whitney U test; [a] Comparison of posttreatment values between groups; [ab] Comparison of pre- and posttreatment values per group.

using the same device in the same manner, but without transferring any laser beams to the aforementioned areas.

The primary outcome of the study was clinical and electrophysiological improvement in CTS symptoms as assessed by the BCTQ, SSS, FSS, and electrodiagnostic studies.

Statistical analysis

Study power and sample size calculation were performed using the Minitab version 16.0 software (Minitab, LLC., Chicago, IL, USA). For a study power of 99% and 5% type 1 error, each group required minimum a total of 21 patients.

Statistical analysis was performed using the IBM SPSS for Windows version 20.0 software (IBM Corp., Armonk, NY, USA). Normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed in mean and standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. Intergroup comparison of the normally distributed qualitative variables was obtained using the independent samples t-test and intergroup comparison of the non-normally distributed qualitative variables were evaluated using the Mann-Whitney U test. The chi-square and Fisher's exact tests were to compare categorical variables. Dependent samples t-test was used in the analysis of intergroup normally distributed repeated measures, while non-normally distributed data were evaluated using the Wilcoxon signed-rank test. The McNemar test was used to analyze categorical data. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 42 patients with mild-to-moderate CTS completed the study, 22 received LLLT (therapy group) and 20 received sham LLLT (control group). No side effects of treatment were recorded. There was no significant difference in the age, BMI, affected hand and dominance, symptom duration, occupation requiring repetitive hand movements, and severity of CTS of the patients in the groups (Table 1).

Table 4. Ultrasonographic findings before and after treatment

	Sham LLLT group (n=20)						LLLT group (n=22)							
	Pretreatment			Posttreatment			Pretreatment			Posttreatment				
	n	%	Mean±SD	n	%	Mean±SD	p^{ab}	n	%	Mean±SD	n	%	Mean±SD	p^{ab}	p^{a}
Median nerve CSA (mm^2)			13.8±4.4			13.8±3.9	0.907*			13.0±3.0			11.1±2.5	<0.001*	0.022**
PBFR (mm)			3.9±1.1			3.7±1.1	0.546*			4.1±1.1			3.7±0.9	0.068*	0.840**
Flattening ratio			2.8±0.6			2.8±0.6	0.958*			3.0±0.6			3.2±0.8	0.169*	0.048**
Power Doppler grade														0.021‡	0.475†
0	8	40.0		13	65.0			10	45.5		16	72.7			
1	6	30.0		4	20.0			10	45.5		6	27.3			
2	4	20.0		2	10.0			1	4.5		0	0			
3	2	10.0		1	5.0			1	4.5		0	0			

LLLT: Low-level laser therapy; SD: Standard deviation; CSA: Cross-sectional area; PBFR: Palmar bowing of the retinaculum; * Paired samples t-test; ** Independent samples t-test; † Chi-square test ([a] Comparison of post-treatment values between groups); ‡ McNemar test ([ab] Comparison of pre- and posttreatment values per group).

Symptoms of nocturnal paresthesia significantly improved in both groups (LLLT p=0.008, sham LLLT p=0.031) with no significant difference between the groups (p=0.49). On the other hand, there was a significant reduction in the number of patients with a positive Phalen's test in the therapy group (p=0.031), compared to control group, and pain was also significantly reduced only in the therapy group (p=0.031) (Table 2). There was no statistically significant difference between the groups in terms of other clinical and physical examination findings (p≥0.05).

The decrease in SSS after treatment was significant in the LLLT group (p<0.001), but not in the control group (p=0.947). Similarly, there was a significant decrease in the FSS after treatment in the laser group (p<0.001), which was also not the case in the control group (p=0.500).

There was no significant difference between the groups in terms of median nerve DML, motor NCV, CMAP amplitude, and median nerve F latency. However, median nerve SCVs (SCV palm-wrist p=0.008, SCV third digit-wrist p=0.030) in the LLLT group significantly improved with treatment (Table 3). Median nerve palm-wrist sensory amplitude increased in both groups, indicating no significant intergroup difference. The ulnar nerve fifth finger DSL increased compared to baseline (p=0.002) in the sham group alone. No statistically significant change was found in the other nerve conduction studies (p≥0.05).

Following treatment with LLLT, the US CSA and vascularity of the median nerve significantly reduced (p<0.001 and p=0.021, respectively). Furthermore, the improvement in the FR of the median nerve was significantly more in the LLLT group, compared to the sham LLLT group (p=0.048). There was no significant change in US findings of the sham LLLT group (Table 4). Changes in PBFR after treatment were statistically non-significant in both groups (Sham LLLT p=0.546, LLLT p=0.068).

DISCUSSION

Although the role of LLLT as an effective PT modality in the treatment of CTS has previously been studied, it still remains a subject under debate. In this study, as well as investigating the clinical and electrodiagnostic outcomes of patients with CTS treated with LLLT, we investigated the changes in US imaging as a result of this treatment, which is an area that has not been fully investigated in the literature.

Lasers (light amplification by stimulated emission of radiation) are a source of light which generate electromagnetic radiation and have a non-thermal, photochemical effect on biological systems; the light is absorbed and causes chemical change.[29,30] Low-level laser therapy increases mitochondrial adenosine triphosphate production and oxygen consumption and can provide cells with protection against nitric oxide-induced cell death.[31] Although the therapeutic mechanism of LLLT has not been completely understood yet, its possible anti-inflammatory, analgesic, and neuroregenerative properties in the clinical setting have been demonstrated in several studies.[14-17] The results of our study showed that LLLT was no superior to sham LLLT in reducing typical symptoms of nocturnal paresthesia in mild-to-moderate CTS, but was significantly better at improving pain, symptom severity, and functionality with a positive effect on sensory nerve conduction studies.

The results of this study regarding the CTS symptom severity, functionality, and electrodiagnostic findings following LLLT are consistent with some previous randomized studies, but not consistent with some others. Similar to our study, a meta-analysis by Li et al.[32] of seven randomized trials concluded that LLLT had a positive outcome on hand grip, hand pain and SNAPs three months after treatment in mild-to-moderate CTS.[32] However, the authors also reported that important LLLT factors such as wavelength, power, frequency, irradiating the entire transverse carpal ligament versus irradiating certain predefined points on the wrist still need to be investigated to decipher the most optimal treatment protocol. The variability of these factors from study to study may explain the contradictory findings regarding the effectiveness of LLLT in CTS.[10,18,19] This variability may also explain why another meta-analysis by Bekhet et al.,[33] which included eight randomized studies (seven of which were the same as the studies included in the meta-analysis by Li et al.[32]) published only a year later, concluded that LLLT was superior to placebo

in improving grip strength in mild-to-moderate CTS, but not in improving functional status or pain. Furthermore, a very recent meta-analysis conducted by Cheung et al.,[34] which included six randomized-controlled studies comparing LLLT to splinting in the treatment of CTS, found that clinical reduction in pain was not significantly greater in patients receiving LLLT plus splinting compared to splinting alone. The authors also concluded that LLLT plus splinting was not superior to splinting alone in terms of symptom severity and functional status.

In our study, the improvement in nocturnal paresthesia seen in both patient groups is believed to be a result of consistent nocturnal use of a wrist orthosis in both groups to reduce the pressure on the median nerve by increasing the CT volume. On the other hand, there was a significant improvement in the Phalen's test, pain and both the SSS and FSS in the LLLT group compared to the control group, suggesting that that the patients showed both functional and symptomatic improvement after LLLT. The positive effect of LLLT on clinical parameters can be attributed to the aforementioned anti-inflammatory and analgesic effects of the laser application. The main pertinent differences between our study and previous studies comparing LLLT plus splinting to sham LLLT plus splinting, in which there was no significant difference in the clinical features of study and control groups, is that the total dosage of laser was lower, but more points over the CT were treated in our study. While we administered 0.8 J/2 min per point over five points per session, in the study by Evcik et al.,[10] 7 J/2 min per point over two points per session of LLLT was administered.[10] In the study by Yagci et al.,[13] a total of 8.1 J over three points was administered per session and 10 J/cm^2 by Barbosa et al.[18] The follow-up time was also longer in the latter two studies; i.e., three months and six weeks respectively. This finding highlights that heterogeneity in laser dosage, the number of points treated, and follow-up time are possible factors affecting the variability in study outcomes.

Similarly, electrophysiological studies in our study revealed a significant improvement in sensory nerve conduction studies in the therapy group. This is consistent with the study findings of Shooshtari et al.[11] in which transcarpal SCV and median sensory latencies significantly improved in the LLLT group (9-11 J/cm^2), but not in the sham LLLT group.[11] On the other hand, in our study, the improvement in motor nerve conduction studies after treatment was non-significant, which in contrast to the findings of Fusakul et al.[9] who compared LLLT (18 J/session) and splinting to sham LLLT and splinting in the treatment of CTS and found that distal motor latency of the median nerve improved at 12 weeks of follow-up. This difference may be due to the higher dosage of LLLT applied in this study. In addition, biophysical differences between sensory and motor fibers suggest that sensory fibers are more susceptible to mechanical stress;[35] therefore, the benefits of LLLT in these fibers may become evident sooner. Probably, a longer follow-up and repeat ENMG studies may have detected similar improvements in the motor fibers of the median nerve. We do not have a conclusive explanation to some findings in this study: the ulnar nerve fifth finger DSL increased after treatment in the sham group compared to LLLT group ($p=0.002$), which may be a coincidental result.

In recent years, the use of US in the diagnosis of CTS has been increasing. Compression and swelling of the median nerve result in an increase in the median nerve CSA on diagnostic US in CTS cases compared to healthy controls.[36] Furthermore, many studies claim that median nerve CSA is the most sensitive US measurement in the diagnosis of CTS.[7] In our study, a significant reduction in CSA was seen following treatment with LLLT, suggesting that the anti-inflammatory effects of LLLT may have reduced perineural edema.

Considering the pathophysiology of CTS, an increase in median nerve intraneural microvascularization may be expected due to inflammation and compression. Assessment of the vascularity of the median nerve using color and power Doppler as an adjunct in the diagnosis of CTS has becoming increasingly important; however, its sensitivity, specificity, and accuracy when used alone in the diagnosis CTS is still questionable at 31.8%, 87.5%, and 55.3%, respectively.[7] On the other hand, when power Doppler is combined with median nerve CSA measurements, the sensitivity and specificity of a diagnosis of CTS have been shown to increase to over 90% with a positive correlation between them.[37] One group of researchers in

this field suggested that assessment of vascularity with color Doppler in addition to CSA results in improved sensitivity and specificity equaling that of electrodiagnostic studies.[38] In our study, vascularization of the median nerve significantly decreased following treatment with LLLT compared to the control group, and this was considered being in favor of the improvement. The results of our study suggest that intraneural vascularity is also reduced as a consequence of the anti-inflammatory properties of LLLT.

Furthermore, the improvement in median nerve FR was significantly more in the LLLT group, compared to the sham LLLT group after treatment. Early studies on the role of FR in the diagnosis of CTS reported a sensitivity ranging between 38 and 65%.[39,40] However, this topic continues to be debated with a very recent study by Chang et al.[36] who found no significant difference in FR of those with a diagnosis of CTS compared to a group of healthy volunteers. Another study showed no significant correlation between FR and electrodiagnostic values.[41] A consensus regarding the optimal cut-off values for FR still remains to be elucidated. Similarly, in this study, PBFR remained unchanged following treatment. Studies to date have shown that PBFR increases in CTS compared to healthy controls with a positive correlation with electrophysiological abnormalities; however, this remains contested currently.[7,41,42]

Nonetheless, there are some limitations to this study. We believe that a longer follow-up period and a larger sample size would have allowed the opportunity to investigate the long-term clinical, electrophysiological and US outcomes of treatment of CTS with LLLT.[43] In addition, assessment of the hand and finger grip strengths would have provided a clinical evaluation of the motor function of the median nerve in response to treatment.

In conclusion, our study provides new US data demonstrating LLLT efficacy in addition to the clinical and electrophysiological improvement. We believe that LLLT may be recommended as an alternative PT modality in the conservative treatment of CTS. Future studies should concentrate on determining the optimal wavelength, power, and anatomical application of LLLT while treating CTS and long-term treatment outcomes.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

This study was funded by the Başkent University Research Fund (Project no KA15/159).

REFERENCES

1. Werner RA, Andary M. Carpal tunnel syndrome: Pathophysiology and clinical neurophysiology. Clin Neurophysiol 2002;113:1373-81.
2. MacDermid JC, Wessel J. Clinical diagnosis of carpal tunnel syndrome: A systematic review. J Hand Ther 2004;17:309-19.
3. McDonagh C, Alexander M, Kane D. The role of ultrasound in the diagnosis and management of carpal tunnel syndrome: A new paradigm. Rheumatology (Oxford) 2015;54:9-19.
4. Cartwright MS, Hobson-Webb LD, Boon AJ, Alter KE, Hunt CH, Flores VH, et al. Evidence-based guideline: Neuromuscular ultrasound for the diagnosis of carpal tunnel syndrome. Muscle Nerve 2012;46:287-93.
5. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Nasr A. Ultrasound assessment of the median nerve: A biomarker that can help in setting a treat to target approach tailored for carpal tunnel syndrome patients. Springerplus 2015;4:13.
6. Tezcan S, Ulu Ozturk F, Uslu N, Nalbant M, Umit Yemisci O. Carpal tunnel syndrome: Evaluation of the effects of low-level laser therapy with ultrasound strain imaging. J Ultrasound Med 2019;38:113-22.
7. Ng AWH, Griffith JF, Lee RKL, Tse WL, Wong CWY, Ho PC. Ultrasound carpal tunnel syndrome: Additional criteria for diagnosis. Clin Radiol 2018;73:214.e11-214.e18.
8. Bakhtiary AH, Rashidy-Pour A. Ultrasound and laser therapy in the treatment of carpal tunnel syndrome. Aust J Physiother 2004;50:147-51.
9. Fusakul Y, Aranyavalai T, Saensri P, Thiengwittayaporn S. Low-level laser therapy with a wrist splint to treat carpal tunnel syndrome: A double-blinded randomized controlled trial. Lasers Med Sci 2014;29:1279-87.
10. Evcik D, Kavuncu V, Cakir T, Subasi V, Yaman M. Laser therapy in the treatment of carpal tunnel syndrome: A randomized controlled trial. Photomed Laser Surg 2007;25:34-9.
11. Shooshtari SM, Badiee V, Taghizadeh SH, Nematollahi AH, Amanollahi AH, Grami MT. The effects of low level laser in clinical outcome and neurophysiological results of carpal tunnel syndrome. Electromyogr Clin Neurophysiol 2008;48:229-31.
12. Lazovic M, Ilic-Stojanovic O, Kocic M, Zivkovic V, Hrkovic M, Radosavljevic N. Placebo-controlled investigation of

low-level laser therapy to treat carpal tunnel syndrome. Photomed Laser Surg 2014;32:336-44.
13. Yagci I, Elmas O, Akcan E, Ustun I, Gunduz OH, Guven Z. Comparison of splinting and splinting plus low-level laser therapy in idiopathic carpal tunnel syndrome. Clin Rheumatol 2009;28:1059-65.
14. Rochkind S, Vogler I, Barr-Nea L. Spinal cord response to laser treatment of injured peripheral nerve. Spine (Phila Pa 1976) 1990;15:6-10.
15. Honmura A, Ishii A, Yanase M, Obata J, Haruki E. Analgesic effect of Ga-Al-As diode laser irradiation on hyperalgesia in carrageenin-induced inflammation. Lasers Surg Med 1993;13:463-9.
16. Jarvis D, MacIver BM, Tanelian DL. Electrophysiologic recording and thermodynamic modeling demonstrate that helium-neon laser irradiation does not affect peripheral Adelta- or C-fiber nociceptors. Pain 1990;43:235-42.
17. Lee G, Wong E, Mason DT. New concepts in pain management and in the application of low-power laser for relief of cervicothoracic pain syndromes. Am Heart J 1996;132:1329-34.
18. Barbosa RI, Fonseca Mde C, Rodrigues EK, Tamanini G, Marcolino AM, Mazzer N, et al. Efficacy of low-level laser therapy associated to orthoses for patients with carpal tunnel syndrome: A randomized single-blinded controlled trial. J Back Musculoskelet Rehabil 2016;29:459-66.
19. Rayegani SM, Bahrami MH, Eliaspour D, Raeissadat SA, Shafi Tabar Samakoosh M, Sedihgipour L, et al. The effects of low intensity laser on clinical and electrophysiological parameters of carpal tunnel syndrome. J Lasers Med Sci 2013;4:182-9.
20. Tascioglu F, Degirmenci NA, Ozkan S, Mehmetoglu O. Low-level laser in the treatment of carpal tunnel syndrome: Clinical, electrophysiological, and ultrasonographical evaluation. Rheumatol Int 2012;32:409-15.
21. Stevens JC. AAEM minimonograph #26: The electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine. Muscle Nerve 1997;20:1477-86.
22. Levine DW, Simmons BP, Koris MJ, Daltroy LH, Hohl GG, Fossel AH, et al. A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Joint Surg [Am] 1993;75:1585-92.
23. Sezgin M, Incel NA, Serhan S, Camdeviren H, As I, Erdoğan C. Assessment of symptom severity and functional status in patients with carpal tunnel syndrome: Reliability and functionality of the Turkish version of the Boston Questionnaire. Disabil Rehabil 2006;28:1281-5.
24. El Miedany Y. Carpal tunnel syndrom. Musculoskeletal ultrasonography in rheumatic diseas. 1st ed. Springer International Publishing; 2015. p. 207-238 1976.
25. Altinok T, Baysal O, Karakas HM, Sigirci A, Alkan A, Kayhan A, et al. Ultrasonographic assessment of mild and moderate idiopathic carpal tunnel syndrome. Clin Radiol 2004;59:916-25.
26. Yurdakul OV, Mesci N, Çetinkaya Y, Geler Külcü D. Diagnostic significance of ultrasonographic measurements and median-ulnar ratio in carpal tunnel syndrome: Correlation with nerve conduction studies. J Clin Neurol 2016;12:289-94.
27. Dejaco C, Stradner M, Zauner D, Seel W, Simmet NE, Klammer A, et al. Ultrasound for diagnosis of carpal tunnel syndrome: comparison of different methods to determine median nerve volume and value of power Doppler sonography. Ann Rheum Dis 2013;72:1934-9.
28. Burke DT, Burke MM, Stewart GW, Cambré A. Splinting for carpal tunnel syndrome: In search of the optimal angle. Arch Phys Med Rehabil 1994;75:1241-4.
29. Maiman TH. Stimulated optical radiation in Ruby. Nature 1960;187:493-4.
30. Lin F, Josephs SF, Alexandrescu DT, Ramos F, Bogin V, Gammill V, et al. Lasers, stem cells, and COPD. J Transl Med 2010;8:16.
31. Farivar S, Malekshahabi T, Shiari R. Biological effects of low level laser therapy. J Lasers Med Sci 2014;5:58-62.
32. Li ZJ, Wang Y, Zhang HF, Ma XL, Tian P, Huang Y. Effectiveness of low-level laser on carpal tunnel syndrome: A meta-analysis of previously reported randomized trials. Medicine (Baltimore) 2016;95:e4424.
33. Bekhet AH, Ragab B, Abushouk AI, Elgebaly A, Ali OI. Efficacy of low-level laser therapy in carpal tunnel syndrome management: A systematic review and meta-analysis. Lasers Med Sci 2017;32:1439-48.
34. Cheung WKW, Wu IXY, Sit RWS, Ho RST, Wong CHL, Wong SYS, et al. Low-level laser therapy for carpal tunnel syndrome: Systematic review and network meta-analysis. Physiotherapy 2020;106:24-35.
35. Lin CS, Kuwabara S, Cappelen-Smith C, Burke D. Responses of human sensory and motor axons to the release of ischaemia and to hyperpolarizing currents. J Physiol 2002;541:1025-39.
36. Chang YW, Hsieh TC, Tzeng IS, Chiu V, Huang PJ, Horng YS. Ratio and difference of the cross-sectional area of median nerve to ulnar nerve in diagnosing carpal tunnel syndrome: A case control study. BMC Med Imaging 2019;19:52.
37. Kutlar N, Bayrak AO, Bayrak İK, Canbaz S, Türker H. Diagnosing carpal tunnel syndrome with Doppler ultrasonography: A comparison of ultrasonographic measurements and electrophysiological severity. Neurol Res 2017;39:126-32.
38. McDonagh C, Alexander M, Kane D. The role of ultrasound in the diagnosis and management of carpal tunnel syndrome: A new paradigm. Rheumatology (Oxford) 2015;54:9-19.
39. Duncan I, Sullivan P, Lomas F. Sonography in the diagnosis of carpal tunnel syndrome. AJR Am J Roentgenol 1999;173:681-4.

40. Buchberger W, Judmaier W, Birbamer G, Lener M, Schmidauer C. Carpal tunnel syndrome: Diagnosis with high-resolution sonography. AJR Am J Roentgenol 1992;159:793-8.
41. Roll SC, Evans KD, Li X, Freimer M, Sommerich CM. Screening for carpal tunnel syndrome using sonography. J Ultrasound Med 2011;30:1657-67.
42. Kim MK, Jeon HJ, Park SH, Park DS, Nam HS. Value of ultrasonography in the diagnosis of carpal tunnel syndrome: Correlation with electrophysiological abnormalities and clinical severity. J Korean Neurosurg Soc 2014;55:78-82.
43. Franke TP, Koes BW, Geelen SJ, Huisstede BM. Do patients with carpal tunnel syndrome benefit from low-level laser therapy? A systematic review of randomized controlled trials. Arch Phys Med Rehabil 2018;99:1650-9.e15.