

ABSTRACT: Several studies have suggested that low-level laser therapy (LLLT) is effective in patients with carpal tunnel syndrome (CTS). In a double-blind randomized controlled trial of LLLT, 15 CTS patients, 34 to 67 years of age, were randomly assigned to either the control group ($n = 8$) or treatment group ($n = 7$). Both groups were treated three times per week for 5 weeks. Those in the treatment group received 860 nm gallium/aluminum/arsenide laser at a dosage of 6 J/cm² over the carpal tunnel, whereas those in the control group were treated with sham laser. The primary outcome measure was the Levine Carpal Tunnel Syndrome Questionnaire, and the secondary outcome measures were electrophysiological data and the Purdue pegboard test. All patients completed the study without adverse effects. There was a significant symptomatic improvement in both the control ($P = 0.034$) and treatment ($P = 0.043$) groups. However, there was no significant difference in any of the outcome measures between the two groups. Thus, LLLT is no more effective in the reduction of symptoms of CTS than is sham treatment.

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DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL OF LOW-LEVEL LASER THERAPY IN CARPAL TUNNEL SYNDROME

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Carpal tunnel syndrome (CTS) is very common. In 1999, CTS accounted for over 50% of the total health-care costs associated with mononeuritis and soft-tissue inflammation claims in the United States.¹⁵ The symptoms of CTS arise as a result of compression of the median nerve by surrounding structures in the carpal tunnel. Although surgery is effective in relieving pressure around the nerve, it is not without risk. For those patients whose symptoms and functional impairment are not sufficiently severe, nonsurgical options remain the mainstay of treatment. Although a number of non-surgical treatments including wrist splinting, stretching exercise, and anti-inflammatory medications are available, none has been universally successful. Even with these treatments, many patients are left with recurrent or

persistent symptoms, sometimes lasting for years. Therefore, physical modalities are often used as alternative options. One commonly used modality is low-level laser therapy (LLLT). The safety profile of LLLT has been well established over several decades of use.^{6,24} When applied to sciatic nerve and spinal cord in rats injured through crushing, LLLT was found to enhance recovery by increasing myelin production and reducing retrograde degeneration of motor neurons.^{33,34} Several human studies evaluating LLLT on patients with CTS also have showed beneficial effects.^{29,31,37} However, these findings are not consistent and are at times contradictory.^{15,39,40} Given the vast economic and personal impact of CTS, a clear answer to the potential role of LLLT is much needed.

Many of the known effects of LLLT, including modulation of fibroblast proliferation and phagocytic cell activation, are of relevance in wound healing^{3,4,19,22,35,38,41} and inflammatory conditions such as rheumatoid arthritis.^{8,9} However, there is little compelling evidence to suggest that it has a beneficial effect on altering peripheral nerve function in humans. Indeed, LLLT irradiation does not change the functional properties of peripheral nerves.^{5,17} Therefore, we hypothesize that LLLT is not effective

Abbreviations: CTS, carpal tunnel syndrome; LLLT, low-level laser therapy; S-MUAP, surface-detected motor unit action potential

Key words: carpal tunnel syndrome; hand function; low-level laser therapy; randomized controlled trial

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in the reduction of pain and paresthesias and does not improve the nerve physiological functions and hand performance in patients with CTS. The purpose of this study was to test this hypothesis.

METHODS

Protocol. Patients were included in the study if they had one of the following constellation of symptoms: (1) numbness and tingling in the median nerve distribution; (2) such sensory symptoms precipitated by repetitive hand activities and relieved by resting, rubbing, and shaking the hand; (3) nocturnal awakening by such sensory symptoms; and (4) weakness of thumb abduction as quantified by using the Medical Research Council scale.²⁶ In addition, these symptoms and signs required support by electrophysiological evidence of focal median nerve compression in the carpal tunnel resulting primarily in conduction slowing or conduction block of the sensory and motor nerve fibers. The ulnar nerve and superficial radial nerve were also evaluated through clinical examination and electrophysiological studies to ensure that the other peripheral nerves innervating the hand were not affected.

Patients were excluded if they had evidence of marked axonal loss. The reason for this exclusion criterion is that those who already had marked axonal loss would not be expected to improve quickly even if pressure around the nerve were relieved. In addition, patients with arthritic diseases, trauma to wrist or arm, and previous carpal tunnel release were also excluded from the study. A careful screen for other neurological conditions including the presence of other peripheral neuropathies was performed by interview and clinical examination. When indicated, further substantiating evidence through electrophysiological studies and other investigations was sought. Patients were asked to refrain from using analgesic medications. They were not given any other treatment for CTS during the course of the study and were advised to continue their normal daily work and recreational activities.

The study was approved by the human research ethics board at the University of Alberta and all subjects gave their informed consent.

Outcome Measures. *Symptom Assessment.* The Levine Carpal Tunnel Syndrome Questionnaire (Levine CTS Questionnaire), a CTS measurement tool with established validity and reliability, was used.^{2,16,20,23} It has been utilized as an outcome measure in many published clinical trials on CTS^{1,7,12,20,21,27,28} and consists of 11 questions assess-

ing the frequency and severity of pain and numbness related to CTS. The severity is quantified on a Likert scale ranging from 1 (none) to 5 (very severe). In addition, there are eight questions assessing hand functions (e.g., writing, opening jars, etc.), with severity ranked from 1 (no difficulty) to 5 (unable to perform).

Objective Hand Functional Performance. This was assessed using the Purdue pegboard test, which evaluates the fine motor skills of the hand. It is a timed test requiring the subjects to place a series of small objects—including pegs, washers, and collars—into small holes at the center of the board. A score is given for the number of pieces correctly placed in the holes within the allotted time. Its test-retest reliability and age-specific normative data have been well documented in many published studies.^{10,13,18,25,32,36}

These tests were administered at baseline, midtreatment, immediately after treatment, and then again 4 weeks after treatment.

Electrodiagnostic Tests. All tests were done using an Advantage EMG machine (Neuroscan, El Paso, Texas). The same experienced electromyographer performed all nerve conduction studies. Electrodiagnostic studies were performed at the same time as the other tests.

Surface stimulation and recording electrodes were used for the sensory and motor nerve conduction tests, employing standard methodology.¹¹ The hand temperature was monitored using an adhesive surface thermistor placed over the thenar eminence throughout the studies to ensure that it was between 32°C and 34°C.

During the sensory nerve conduction studies, the median sensory nerve fibers were stimulated antidromically with a 0.05-ms square pulse at midpalm and wrist with a distance of 7 cm and 14 cm from the recording ring electrode looped around the proximal interphalangeal joint of the third digit. The reference ring electrode was placed around the distal interphalangeal joint. During the motor nerve conduction studies, the median motor nerve fibers were stimulated with a 0.05-ms square pulse at the wrist at a distance of 8 cm proximal to the recording electrode placed over the motor point of the thenar muscles. The reference electrode was placed over the dorsal aspect of the first metacarpophalangeal joint.

Motor unit number estimation was performed on all patients using the multiple-point stimulation technique to ensure that there had not been any significant motoneuronal loss in median-innervated thenar muscles. The method used was the same as

that originally described by Doherty and Brown.¹⁴

Recording. A disposable, self-adhesive surface electrode (Blue Sensor BS3400; Ambu Inc., Linthicum, Maryland), measuring 1 cm × 2.5 cm, was used to detect the maximum M wave and surface-detected motor unit action potential (S-MUAP). The reference electrode was positioned over the first metacarpophalangeal joint. The active electrode was placed over the innervation zone of the thenar muscles where the largest M wave with the shortest rise time was obtained. A 3 cm × 3 cm metal plate was positioned on the back of the hand as a ground. The bandpass filter was set at 5–2000 Hz. The position of the thumb was standardized by taping it to the side of the palm in an adducted position.

Stimulation. Electrical stimulation of the nerve was performed with a hand-held constant-current bipolar surface bar stimulator. The maximum M wave of the median nerve was evoked by stimulating the median nerve at the wrist at 10% above the maximal intensity with a duration of 0.01 ms. Because the median and ulnar nerves are in close proximity in the upper arm, it was necessary to map out the course of the median nerve to avoid costimulation of the ulnar nerve. Coactivation of the ulnar nerve was recognized by (1) an initial positive deflection of the M wave, (2) abduction of the fifth digit, and (3) the radiation of an electrical sensation into the fourth and fifth digits. In earlier experiments, we also corecorded from the hypothenar eminence and found that when the above conditions were avoided, there was no detectable action potential generated by the hypothenar muscles.

Using the same recording electrodes, S-MUAPs with the lowest stimulus thresholds were elicited by stimulation at relatively superficial sites along the course of the median nerve at the wrist and between the elbow and the axilla. Stimulation was performed at 1 Hz, with gradually increasing intensity until the first reproducible, “all-or-none” S-MUAP was evoked. A collected sample of S-MUAPs was stored in computer memory. The mean peak-to-peak amplitude of this sample of S-MUAPs was calculated using “data point-by-data point” summation. The MUNE was obtained using the following equation: peak-to-peak amplitude of the maximum M wave/peak-to-peak amplitude of the average S-MUAP.

Assignment. Each eligible subject was randomly assigned to the treatment or control group. Randomization was done using the random-number generation function in a commercially available software program (Excel; Microsoft Inc., Redmond, Washington). Subjects with odd numbers were assigned to

the treatment group, and those with even numbers were assigned to the control group. A staff person not involved in the rest of the study performed the randomization. The physical therapist administering the treatments was not involved in the outcome measure assessment. Neither the investigators nor the subjects were aware of the treatment assignment.

Interventions and Masking. **Treatment Device.** The Eriel TOP 250 (Coradon Rehabilitation, Calgary, Alberta, Canada), which emits a low-level gallium/aluminum/arsenide (GaAlAs) laser beam with an 860-nm wavelength, was used. A single-probe diode emitting a 60-mW beam with an intensity of 3 J/cm² per second over an area of 0.01 cm² delivered a total dose of 6 J/cm² in 15 s. A sham probe, identical in appearance, was factory fabricated and supplied by the manufacturer. Neither the subjects nor any of the investigators were aware of the identity of the probes. To evaluate the success of blinding, the participants and the investigators were asked at the end of the study to guess which was the active probe.

Treatment Protocol. Each subject received treatments three times a week for 5 weeks. At each treatment session, the subjects and the physical therapist wore protective glasses. Two identical infrared laser probes, “A” being the sham and “B” being the active probe, were used.

To standardize the total dosage that each subject received, a thin clear plastic template with 1-cm × 1-cm grids was placed over the wrist and palm. Each subject’s hand was photocopied to ensure the template was placed at an identical location at each session. A total of 20 sites over and surrounding the carpal tunnel were irradiated with the laser probe.

Statistical Analysis. Statistical analysis was performed using SPSS Statistical Software (SPSS Inc., Chicago, Illinois). Independent Student’s *t*-test was used to compare the physical characteristics of subjects in the different groups. Multivariate analysis of variance (MANOVA) was used to analyze the sensory and motor nerve conduction study parameters (which included distal motor latency, sensory conduction velocity across the carpal tunnel, and negative-peak amplitude of the sensory nerve action potential and M wave) and the Purdue pegboard test scores. The Wilcoxon rank sum test and Mann-Whitney *U* test were used to compare intrasubject and intersubject differences of the Levine CTS Questionnaire scores during and following treatment. Results are expressed as mean ± SD. A *P*-value of <0.05 was deemed statistically significant.

RESULTS

Participant Flow and Follow-up. Based on the selection criteria, 173 patients were found to be eligible; 121 patients either lived outside metropolitan Edmonton or refused to participate, and 37 patients were unable to schedule the time. Fifteen patients volunteered and agreed to participate in the study. The patients ranged in age from 34 to 67 years (46 ± 11 years). Eight patients were randomly assigned to the control and seven to the treatment group. They all completed the entire baseline, midtreatment, and posttreatment assessments. None of the subjects used any analgesic for the duration of the study.

There was no significant difference in the gender and age distribution between those subjects who participated in the study and those who did not. The male-to-female ratio among the nonparticipants was 1:3 and the age distribution was 48 ± 16 years.

Baseline Characteristics. Demographic characteristics of the two groups were very similar. Two men and 6 women were assigned to the control group, whereas 1 man and 6 women were in the treatment group. There was no significant difference in their age range: 50 ± 4 years in the control group versus 43 ± 4 years in the treatment group. The symptom severity subscale score in the Levine CTS Questionnaire was 2.5 ± 0.5 in the control group. It was not significantly different from that of the treatment group (2.5 ± 0.6). Likewise, the functional disability subscale score of the Levine CTS Questionnaire was similar between the two groups (2.3 ± 1.0 in the control group and 1.8 ± 0.5 in the treatment group). Hand dexterity, electrophysiological functions of the motor and sensory nerve fibers, and the motor unit number estimates also were similar. Negative-peak amplitude of the M wave was 14.7 ± 0.5 mV in the control group and 15.2 ± 3.8 mV in the treatment group, and distal motor latency was 4.3 ± 0.4 ms and 4.8 ± 0.9 ms, respectively. Negative-peak amplitude of the sensory nerve action potential was 20 ± 13 μ V in the control group and 22 ± 11 μ V in the treatment group, and conduction velocity across the carpal tunnel was 34 ± 9 m/s and 31 ± 9 m/s, respectively. Based on accepted electrophysiological criteria,³⁰ the severity of median nerve compression in our patients was in the mild to moderate range.

Severity of Axonal Damage to the Median Nerve. The average motor unit number estimates of the 15 subjects was 251 ± 119 . Compared with healthy subjects in a similar age range,¹⁴ no patient had a severely depleted motor unit number. The extent of motor unit depletion was not significantly different

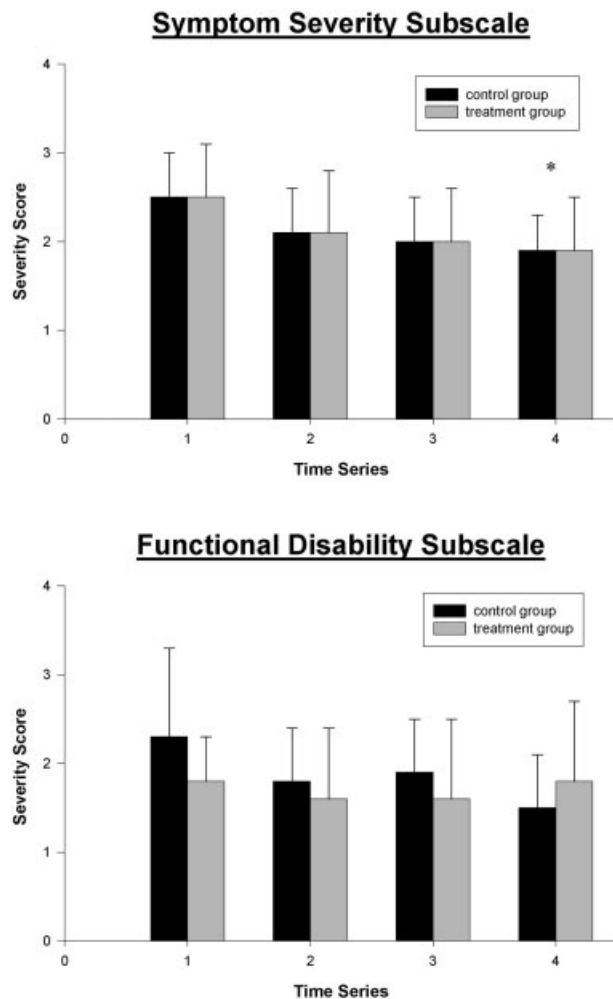


FIGURE 1. Levine Carpal Tunnel Syndrome Questionnaire results. The time points were baseline (1), midtreatment (2), immediately after treatment (3), and 4 weeks after treatment (4). A statistically significant reduction in severity scores is seen in both groups within the symptom severity subscale at 4 weeks after treatment (*). In contrast, the functional disability subscale scores remained unchanged.

between the two groups: 267 ± 137 in the control group and 232 ± 102 in the treatment group.

Treatment-Related Changes. *Change in Symptom Severity.* The Levine CTS Questionnaire scores were not significantly different between the two groups, both at baseline ($P = 0.89$) and at the end of treatment ($P = 0.69$). Interestingly, subjective symptoms significantly improved in both groups 4 weeks after treatment ($P = 0.043$ in the treatment group and $P = 0.034$ in the control group; Fig. 1).

Secondary Outcome Measures. The nature and severity of the electrophysiological abnormalities were very similar between the two groups at baseline. They did not change significantly after 5 weeks of treat-

ment. Change in hand functional performances, as judged by the Purdue pegboard test scores, also did not differ significantly between the two groups. They changed from 72 ± 8 at baseline to 77 ± 10 immediately after treatment in the control group and from 81 ± 9 to 85 ± 11 in the treatment group.

Effectiveness of the Blinding Process. Upon completion of the study, all subjects were asked whether they thought that they received the actual laser treatment. Six of the 8 subjects in the control group believed that they were treated with the active probe, as did 3 of the 7 subjects within the treatment group. In terms of effectiveness of blinding the clinician, the treating therapist thought that probe "A," the sham probe, was the active laser.

DISCUSSION

The principal finding of this study is that LLLT is no more effective in improving CTS symptoms or median nerve and hand functions than is placebo. The results of our study also revealed a significant placebo effect, with symptom improvement being similar in the control and treatment groups. This second finding illustrates the importance of having a control group.

This study has a number of major strengths. First, LLLT turned out to be well suited to a double-blind study design. Both the subjects and the treating therapist performed no better than chance in guessing who was actually receiving laser therapy. This eliminates any potential systematic bias due to the subjective preconception of the subjects or experimenters. This consideration is particularly important in the case of CTS, because its presence is predominantly defined by clinical symptoms. Second, randomization of the groups was successful in that the baseline characteristics of the subjects so assigned to both groups were very similar.

Our findings are somewhat different from those previously reported. Existing data in the literature are very sparse. Only three published studies have evaluated the effectiveness of laser therapy in patients with CTS,^{29,31,37} and all had major limitations. First, the studies by Padua et al.³¹ and Weintraub³⁷ were uncontrolled. This represents a major drawback, as many symptoms of CTS are sensory in nature and are highly subjective. Therefore, the inclusion of a control group and the use of double blinding are crucial. This point is well illustrated by the findings in this study. Second, the treatment dosages and treatment protocols were not clearly described in these studies, so it cannot be determined whether the treatments were performed

properly. Third, a detailed description of the methods used in their electrophysiological studies was absent. This is an important consideration because many factors, including hand temperature, can have a major impact on most electrophysiological parameters. Finally, the results reported in both studies were incomplete. For example, the exact extent of symptom improvement and the variance of treatment responses were not reported in either study.

A double-blind randomized crossover controlled trial was recently published by Naesar et al.²⁹ on patients with mildly to moderately severe CTS. However, in that study, a significant treatment effect was found only after those patients who also showed a response to sham treatment had been excluded. Because placebo effect is a well-known phenomenon, as demonstrated by this and many previous studies, the exclusion of such patients could result in major systematic bias. Furthermore, because transcutaneous electrical nerve stimulation was also used in that study, it is impossible to ascertain whether the improvement was indeed from laser therapy.

A limitation of our study is that the treatment protocol was extremely labor intensive. Each subject had to come to the laboratory 3 times per week for 5 weeks, with each session taking 30 min. This limited the number of subjects who were willing to participate. Fortunately, we were able to retain all the subjects, once they had entered into the study, for its full duration. Furthermore, because there was no significant difference in the age and gender distribution between participants and nonparticipants, the subjects in this study are likely representative of the overall group.

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