Low-Intensity Laser Therapy for Painful Symptoms of Diabetic Sensorimotor Polyneuropathy

A controlled trial

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OBJECTIVE — Low-intensity laser therapy (LILT) has been advocated for treatment of chronic pain disorders. Although the mechanism of pain relief is uncertain, this therapy has been suggested for relief of painful symptoms of diabetic sensorimotor polyneuropathy (DSP). The objective of this study was to determine whether LILT relieves the pain of DSP.

RESEARCH DESIGN AND METHODS — We conducted a randomized, double-masked, sham therapy–controlled clinical trial in 50 patients with painful DSP diagnosed with the Toronto Clinical Neuropathy Score. All patients received sham therapy over a 2-week baseline period and were then randomized to receive biweekly sessions of either sham or LILT for 4 weeks. The primary efficacy parameter was the difference in the weekly mean pain scores on a visual analog scale (VAS).

RESULTS — The patients had similar baseline characteristics for pain intensity, HbA_{1c}, and duration of DSP. Both groups noted a decrease in weekly mean pain scores during sham treatment. After the 4-week intervention, the LILT group had an additional reduction in weekly mean pain scores of -1.0 ± 0.4 compared with -0.0 ± 0.4 for the sham group ($P = 0.07$). LILT had no effect on the Toronto Clinical Neuropathy Score, nerve conduction studies, sympathetic skin response, or quantitative sensory testing.

CONCLUSIONS — Although an encouraging trend was observed with LILT, the study results do not provide sufficient evidence to recommend this treatment for painful symptoms of DSP.

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Diabetic sensorimotor polyneuropathy (DSP) is the most common complication of both type 1 and type 2 diabetes. In many patients with DSP, pain will develop at some time during the course of the disease. In a Toronto cohort of diabetic patients being screened for neuropathy, 34% reported painful symptoms referable to their neuropathy (1). Most patients with painful DSP localize their symptoms to the lower extremities, primarily the soles and toes. In addition to discomfort, painful neuropathy symptoms interfere with sleep, decrease quality of life, and increase psychosocial distress (2). The symptoms can be characterized as severe dysesthetic burning with nocturnal worsening (most often in the feet and ankles), cutaneous contact discomfort (allodynia), thermal analgesia, paresthesia, resulting in insomnia, weight loss, anxiety, and depression.

Painful DSP is often resistant to treatment with simple analgesics. Medications such as narcotic analgesics, tricyclic antidepressants, anticonvulsants (phenytoin and gabapentin), phenothiazines, antiarrhythmics, nonsteroidal anti-inflammatory drugs, and opioids have all been used with limited success in treating painful DSP. In addition, adverse effects such as drowsiness, lethargy, and unsteadiness are frequent and limit the use of pharmacologic interventions. Topical treatments such as capsaicin cream have been shown to be effective and without systemic adverse effects in the treatment of painful DSP (3). Nonpharmacologic therapies, such as low-intensity laser therapy (LILT), may also be effective adjunctive or alternative treatments for painful DSP with avoidance of systemic drug adverse effects. However, because of the significant placebo response rate in any clinical trial, nonpharmacologic treatments require careful investigation to ascertain effectiveness.

LILT was pioneered in Europe and Russia in the early 1960s. By definition, LILT takes place at low irradiation intensities. Therefore, it is assumed that any biologic effects are secondary to direct effects of photonic radiation and are not the result of thermal processes (4). Biologic effects attributed to LILT include accelerated recovery from trauma. One report documents considerable improvement in tensile strength of laser-treated wounds at 1 and 2 weeks post-treatment; collagen content significantly increased after 2 weeks (5). Studies of the effects of LILT on the peripheral nervous system have also been encouraging. Transcutaneous low-power laser treatment increased the rate of regeneration of rat facial nerve after crush injury (6). In a double-blind controlled trial, LILT and transcutaneous

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Abbreviations: DSP, diabetic sensorimotor polyneuropathy; LILT, low-intensity laser therapy; NCS, nerve conduction study; QST, quantitative sensory testing; SF-MPQ, Short-Form McGill Pain Questionnaire; SSR, sympathetic skin response; VAS, visual analog scale.

electric nerve stimulation significantly reduced pain scores and improved median sensory latency in patients with carpal tunnel syndrome (7). Pinheiro et al. (8) treated patients with disorders of maxillofacial pain, including trigeminal neuralgia, with laser therapy in a nonrandomized, unblinded study and demonstrated a reduction of painful symptoms.

The mechanism whereby LILT relieves pain is unknown. In the case of neuropathic pain, the analgesic effects of LILT may be due to the local release of neurotransmitters such as serotonin (9), increased mitochondrial ATP production (10), increased release of endorphins (11), or anti-inflammatory effects (12). LILT has previously been tested in a double-blind, placebo-controlled trial in diabetic patients with foot ulcers or gangrene (13). Athermic laser irradiation was found to induce a significant increase in skin microcirculation, as measured by infrared thermography, in patients with diabetic microangiopathy.

Although the exact mechanism of LILT remains obscure, an effective nonpharmacologic treatment for painful DSP would significantly improve patient care. We tested the hypothesis that LILT relieves neuropathic pain symptoms caused by diabetes.

RESEARCH DESIGN AND METHODS

The study was conducted at the Toronto University Health Network in the Diabetic Neuropathy Research Clinic from October 2000 to February 2001. Approval from the University Health Network Research Ethics Board was obtained before commencing the study. Informed consent was obtained from each subject before enrollment.

A total of 50 patients with painful DSP were enrolled in the study. Eligible patients included men or women aged ≥18 years who had DSP for at least 3 months. Diagnosis of DSP was based on the Toronto Clinical Neuropathy Score (Table 1). It was required that pain be present in both feet and significant enough to score ≥4 on the visual analog scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) (14). The use of analgesic or adjuvant analgesic medications (e.g., opiates, antidepressants, anticonvulsants, local anesthetics) was allowed but was unchanged for at least 4 weeks before entering the study and for the duration of the study. Patients were excluded from the study if they had unstable medical conditions (e.g., malignancy, active/untreated thyroid disease) or other neurologic diseases that would confound assessment of neuropathy. Other exclusion criteria included pregnancy, metallic implants, alcohol or illicit drug abuse, and other severe pain symptoms that may confound assessment or self-evaluation of pain secondary to DSP.

Table 1—*Toronto Clinical Neuropathy Score*

Symptom scores	Reflex scores	Sensory test scores
Foot pain	Knee reflexes	Pinprick
Numbness	Ankle reflexes	Temperature
Tingling		Light touch
Weakness		Vibration
Ataxia		Position sense
Upper limb symptoms		

Symptom scores: present = 1, absent = 0; reflex scores: absent = 2, reduced = 1, normal = 0; sensory test scores: abnormal = 1, normal = 0; total scores range from normal = 0 to maximum of 19.

The study was a randomized, double-masked, sham-controlled, parallel-group, single-center study to determine the efficacy and safety of LILT (Theralase Model TLC 5000; Theralase, Toronto, Canada) in 50 patients (25 per group) with painful DSP.

The LILT device had a wavelength of 905 nm and an average power of 0–60 mW. All LILT treatments were for 5 min per site. Two of four instruments were modified by the manufacturer to prevent generation of laser energy. Externally, the instruments were indistinguishable. The output of the laser instruments was measured and recorded by the project administrator on a weekly basis.

Medical history, demographics, physical and neurologic examination were initially performed on all eligible patients. Quantitative sensory testing (QST) and nerve conduction studies (NCSs) were performed, and HbA_{1c} was measured. QST testing included a 10-g Semmes-Weinstein monofilament examination, vibration perception thresholds, cooling-detection thresholds, and heat-pain thresholds. Conventional NCS were administered using a standard testing protocol, and temperature was maintained at >31°C in the legs. Studies included testing of bilateral peroneal motor nerves, sural sensory nerves, and sympathetic skin response (SSR) in the lower limb. QST and NCSs were conducted by an independent observer who was masked to all other results.

All subjects received sham laser therapy during the first 2 weeks of the study and were then randomized to receive either active laser or sham laser therapy over the next 4-week period. Treatment was withdrawn over the final 2 weeks. Treatments were administered twice weekly and were applied to an area of pain along the sole or dorsum of the foot. The instrument has five prongs covering a 6-cm-diameter area of skin. The laser was applied to two painful sites on each foot for a period of 5 min. The trial was double-blinded because neither the patients nor the treating and evaluating clinicians knew which laser was active and which was sham. The VAS, SF-MPQ, and patient global impression of change were performed weekly throughout the study. Neurologic examination, NCSs, QST, and Quality of Life Assessment (SF-36) were performed in all patients upon entry into the study and after the treatment phase (week 6).

The primary efficacy parameter was the change in weekly mean VAS score before (week 2) and after (week 6) active/sham laser treatment. Secondary parameters included changes in Toronto Clinical Neuropathy Score, NCS parameters, QST, SSR parameters and SF-MPQ before and after treatment.

Statistical analyses

Statistical analyses were performed with JMP software (version 5 for Macintosh 2001–2002). The primary analysis compared the final weekly mean pain scores (VAS) between treatment groups using ANOVA. Changes in patient global impression of change was analyzed using the Cochran-Mantel-Haenszel procedure. Responder analysis was performed with responders defined as patients having ≥50% reduction in pain.

Table 2—*Baseline demographics of 50 patients with painful DSP*

	Sham therapy	LILT
n	25	25
Sex (men/women)*	23/2	11/14
Type of diabetes (1/2)	3/22	3/22
Duration of diabetes (years)	14.9 ± 11.9	11.6 ± 8.2
HbA_{1c} (%)	7.8 ± 1.6	8.3 ± 1.6
Duration of pain (years)	4.3 ± 3.1	5.0 ± 3.3
Height (cm)	173.2 ± 7.9	166.6 ± 11.9
Weight (kg)	102.6 ± 29.7	95.5 ± 27.1
Entry pain score	6.9 ± 1.7	7.1 ± 1.9
Post-sham pain score	5.4 ± 2.2	5.8 ± 1.7
Toronto Clinical Neuropathy Score	12.9 ± 3.6	12.0 ± 3.2
Monofilament score toe	4.0 ± 3.4	4.7 ± 2.8
Vibration perception threshold (μ)	123.4 ± 93.3	105.2 ± 80.2
Cooling-detection threshold (°C)	16.4 ± 6.6	13.7 ± 7.8
Heat-pain threshold (°C)	15.3 ± 7.2	16.0 ± 10.6

Data mean ± SD. *Significantly different.

RESULTS — A total of 50 patients (34 men, 16 women) were enrolled in the study. The demographic profile is shown in Table 2. Most patients had type 2 diabetes (88%). Similar baseline demographics were noted in both groups, except more men than women were in the sham group compared with the intervention group (92 vs. 44%, respectively; Table 2). At baseline, there was no statistically significant difference in pain intensity, age, duration or type of diabetes, HbA_{1c}, or duration of DSP between the two groups.

Both groups noted a decrease in weekly mean pain scores after 2 weeks of sham laser therapy (Table 3). After the 4-week intervention (after week 6 of study), pain scores in the sham group remained unchanged (−0.0 ± 0.4), but there was a further reduction in pain scores in the laser-treated group (−1.1 ± 0.4). However, the difference in pain scores between the two groups failed to reach statistical significance ($P = 0.07$).

After the 4-week intervention was completed, the patients underwent a 2-week washout phase with no treatment administered. There was an increase in pain scores for both the sham and LILT groups (0.2 ± 0.4 and 0.5 ± 0.1, respectively); however, the difference between the two groups remained statistically insignificant (Table 3). The pain scores in both groups remained below baseline levels after the 2-week washout phase.

Table 3—*Weekly mean pain ratings on an 11-point VAS*

Visit (weeks)	Sham therapy ($n = 25$)	LILT ($n = 25$)
0	6.9 ± 1.7	7.1 ± 1.9
2*	5.4 ± 2.2	5.8 ± 1.7
6†	5.4 ± 1.9	4.7 ± 2.1
8	5.6 ± 2.3	5.2 ± 2.2

*Randomization visit; †termination of therapy.

Two patients in the LILT-treated group and one patient in the sham group had ≥50% reduction in pain. The Toronto Clinical Neuropathy Score, NCS parameters, SSR parameters, and QST were unchanged during the study (data not shown). The treatment was well tolerated and no adverse effects of LILT were reported.

CONCLUSIONS — Pain is a common manifestation of diabetic neuropathy and can be significantly debilitating. Neuropathic pain is often refractory to multiple pharmacologic interventions, and their use can be limited by adverse effects. Nonpharmacologic treatments lack systemic adverse effects, but efficacy over a simple placebo response optimally should be demonstrated in a fashion similar to the standard for pharmacologic agents, i.e., in controlled clinical trials.

Although the exact mechanism is unknown, LILT has been shown to be beneficial in a number of pain models, including patients with neuropathic pain. For the most part, these studies do not provide level I evidence (15), because they lack randomization, placebo arms, and masked evaluation. The current study rigorously tested LILT in a double-masked, sham-controlled, randomized clinical trial to determine whether this therapy is effective in patients with painful DSP.

As expected, a placebo response was observed in both treatment groups, resulting in an ~20% reduction in pain. Interestingly, the additional 16% reduction in VAS scores (for an overall 34% reduction in pain symptoms) with LILT compared with placebo suggests some efficacy with this treatment. Although statistical significance was not obtained, the absolute change in VAS scores reached a clinically meaningful level if the change was compared with the prestudy baseline level, i.e., incorporating the placebo response.

The study results, demonstrating clinically significant pain relief in all patients regardless of treatment arm, highlight the importance of including placebo/sham groups in clinical research trials to determine whether a proposed treatment is effective. Only when the intervention is tested against placebo/sham can one discriminate between treatment and placebo effects in trials using subjective end points. Therefore, uncontrolled studies reporting benefits with laser therapy must be interpreted with caution.

In this study, randomization produced a significant difference in the proportion of men and women in each group. One might hypothesize that differences in sex response to placebo may have confounded the results. Two large meta-analyses have been conducted investigating sex response rates to placebo in patients with pain (16) and depressive disorder (17). Both studies concluded that sex does not predict placebo response or duration.

Although the study results showed only a trend to improvement with LILT, no significant adverse effects were reported. In addition, there was no concern about treatment interactions in patients on multiple medications, and therefore, LILT could be offered safely to patients with a wide spectrum of comorbid disease. Consequently, a cost-benefit assessment may favor the use of LILT, because the small benefit observed may be helpful in patients with painful DSP, given that there is very low risk, if any, associated with the treatment.

Objective clinical and electrophysi-

ologic testing failed to detect a benefit with LILT, as expected, because the study was conducted over a short period of time with a relatively small number of patients. In addition, the potential benefit of LILT may be restricted to small nerve fibers, which are difficult to assess accurately. More definitive results might have been obtained with a larger sample size as well as more frequent and/or longer duration of laser treatments. Nevertheless, patients are often unable to comply with more frequent or longer visits. If LILT was proven to be effective in future controlled studies, the design of home laser equipment might be advantageous to facilitate patient compliance.

Although this study failed to demonstrate a significant improvement in painful symptoms of DSP with LILT, the observed trend warrants further investigation. We believe that further studies would be worthwhile because painful DSP is common, no significant adverse effects were observed with LILT treatment, and current pharmacologic treatments are variably effective.

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