



A Pilot Study to Evaluate the Efficacy of Class IV Lasers on Non-Healing Neuroischemic Diabetic Foot Ulcers in Patients With Type 2 Diabetes

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Diabetic foot ulcers (DFUs) represent a disabling complication of diabetes that has a devastating impact on the quality of life and predict lower-limb amputation and premature mortality (1). Despite best practice, 30–40% of DFUs do not heal within 12–20 weeks (2). Novel therapeutic agents have been tested in clinical trials and it has been estimated that ~30–50% of patients with neuropathic DFUs receiving these new treatments have healed by 12–20 weeks (3). Laser therapy, delivered with devices emitting one or two wavelengths, has been reported as an adjunctive procedure that promotes the healing of chronic diabetic wounds by increasing the blood flow and the release of growth factors and by reducing the inflammation (4).

In this pilot study, we have been the first to investigate the efficacy of an advanced class IV laser (emitting four wavelengths) on Wagner stage 1 and 2 neuroischemic DFUs of five patients with type 2 diabetes who were **nonresponsive** to conventional treatment for at least 12 weeks. Laser treatment was delivered once a week prior to standard care and dressing. As a control we selected patients with similar DFUs and clinical characteristics treated within our department with standard care. In the laser-treated group, age was 58.2 ± 3.6 years (mean \pm SEM, range 47–66) and mean duration of diabetes was

20.4 ± 2.1 years. At the time of enrollment, glycosylated hemoglobin (HbA_{1c}) was $9.0 \pm 0.8\%$ (74.6 ± 8.4 mmol/mol). All laser-treated patients had preserved renal function (estimated glomerular filtration rate [eGFR] 72 ± 8.3 mL/min) and moderate to severe peripheral artery disease, defined as 20–49% and 50–99% diameter reduction in at least one of the arterial segments from aorto-iliac to popliteal segments on an arterial duplex scan. The mean size of the ulcers was 2.4 ± 1.0 cm². The control group of six patients with type 2 diabetes received standard care and had similar ulcer duration and size; comparable glycemic control, age, diabetes duration, and eGFR; and similar degree of peripheral artery disease (Table 1). Standard care for DFUs, including antibiotic treatment, dressing, and off-loading, was similar in both groups. Within the 12-week follow-up, four of five laser-treated patients (80%) had a complete ulcer resolution (most ulcers healed after 4.6 weeks). In the control group, no ulcer healing occurred by week 12.

A limited number of small clinical trials and case studies evaluating the effects of laser devices with lower power and one or two wavelengths on DFUs have previously reported positive outcomes (4). However, because of the heterogeneity in the methodology, findings from these studies have not been consistent. The

laser used in this pilot study is the first example of a high-powered device with four wavelengths concomitantly acting on multiple metabolic processes that accelerate the wound healing: stimulation of cytochrome-C oxidase, an increase in angiogenesis, and improvement in blood perfusion (5).

Taking into consideration the limitations of this proof-of-concept study, our findings indicate that laser therapy delivered by a class IV laser can significantly **impact** the healing process of neuroischemic DFUs refractory to standard treatment. Randomized controlled clinical trials with this new laser device in larger populations are required to confirm our results.

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Table 1—Patients characteristics and study outcomes

	Laser + standard treatment	Standard treatment
<i>n</i>	5	6
Sex (male/female)	5/0	5/1
Age (years)	58.2 ± 3.6	63.2 ± 5.1
Duration of diabetes (years)	20.4 ± 2.1	13.8 ± 3.0
HbA _{1c} [% (mmol/L)]	9.0 ± 0.8 (74.6 ± 8.4)	8.1 ± 0.9 (65.2 ± 10.3)
eGFR (mL/min)	72 ± 8.3	65.2 ± 10.3
Duration of ulcers (weeks)	18 ± 2.3	17.3 ± 1.2
Ulcer area (cm ²)	2.4 ± 1.0	2.2 ± 0.5
Patients with complete healing in <12 weeks	4/5	0/6

Data are *n* or mean ± SEM.

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References

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet* 2005;366:1719–1724
2. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. *Diabetes Care* 2007;30:660–663
3. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. *Diabetes Care* 2002;25:1835–1839
4. Beckmann KH, Meyer-Hamme G, Schröder S. Low level laser therapy for the treatment of diabetic foot ulcers: a critical survey. *Evid Based Complement Alternat Med* 2014;2014:626127
5. Vladimirov YA, Osipov AN, Klebanov GI. Photobiological principles of therapeutic applications of laser radiation. *Biochemistry (Mosc)* 2004;69:81–90

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AUTHOR QUERIES

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