The Journal of Foot & Ankle Surgery 58 (2019) 1077–1080

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

# Erbium: Yttrium Aluminum Garnet Laser Accelerates Healing in Indolent Diabetic Foot Ulcers

Matthew J. Johnson, DPM[1], Peter A. Crisologo, DPM, AACFAS[2], David H. Truong, DPM, MS[1], Dane K. Wukich, MD[3], Orhan K. Oz, MD[4], Javier La Fontaine, DPM, MS, FACFAS[5], Lawrence A. Lavery, DPM, MPH, FACFAS[5]

[1] *Fellow, Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[2] *Research Fellow, Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[3] *Professor and Chairman, Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[4] *Professor, Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[5] *Professor, Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*

ARTICLE INFO

*Level of Clinical Evidence:* 4

*Keywords:*
healing
debridement
laser
percent wound area reduction
treatment

ABSTRACT

The objective of the study was to evaluate the effect of the erbium:yttrium aluminum garnet (YAG) laser on diabetic foot ulcers (DFUs) that had not responded to standard care. We retrospectively evaluated 22 nonhealing DFUs that received at least 4 weeks of standard wound care, demonstrated poor healing response, and subsequently were treated with an erbium:YAG laser. We measured the percent wound area reduction (PWAR) for the 4 weeks before initiating laser therapy and the PWAR for 4 weeks after the initiation of laser therapy. Erbium:YAG laser treatment consisted of 2 components: debridement and resurfacing. The laser settings were the same for all treatments. We used the paired *t* test to compare pretreatment with posttreatment wound area reduction. During the 4-week period before the initiation of laser therapy, the average PWAR was −33.6%. Four weeks after initiating treatment with the erbium:YAG laser, the average PWAR was 63.4% ($p = .002$) and 72.7% of wounds had ≥50% PWAR. By 12 weeks, 50% of wounds had healed. Erbium:YAG laser therapy accelerated DFU healing in a cohort of patients with ulcers that had been unresponsive to standard of care therapy.



Diabetic foot ulcers (DFUs) are notoriously difficult to heal. Even in well-controlled clinical trials evaluating advanced DFU treatments, with very selective patient populations in the control and treatment arms, only 18% to 36% and 30% to 62% of DFUs heal, respectively (1–4). The annual cost of DFUs has been estimated to be $9 to $13 billion (5). Nonhealing ulcers are a precursor to infection and amputation and dramatically impact the quality of life of patients (6). Given this, finding innovative approaches to improve ulcer outcomes is a vital part of reducing the human and economic burden of DFUs.

One opportunity to improve outcomes may be to identify more effective methods of ulcer debridement. One possibility is to convert chronic wounds to acute wounds and restart the wound-healing process (7). Wound healing is accelerated when debridement is performed frequently, and a higher proportion of wounds fail when debridement is not provided (8). This is believed to be the result of the devitalized tissue in a wound that provides a safe haven for bacterial proliferation and inhibits the body's cellular defenses to fight infection (9). There are several human and animal studies using a laser to debride chronic wounds that show accelerated wound healing (10–15). There are also controlled studies showing the efficacy of lasers in wound healing (16,17); however, laser therapy for DFUs is rarely discussed. The purpose of this study was to evaluate the effectiveness of high-intensity erbium:yttrium aluminum garnet (YAG) laser to treat indolent DFUs.

## Patients and Methods

This study was approved by the institutional review board at our university medical center. The medical records of 34 consecutive patients who were treated at our university hospital wound clinic during a 6-month period from July 2018 to December 2018 were reviewed. Inclusion criteria included patients with a diagnosis of diabetes mellitus based on American Diabetes Association criteria (18), age between 18 and 89 years, and foot and/or ankle ulcers that received at least 4 weeks of standard wound care, demonstrated poor healing response (i.e., the wound area [in $cm^2$] had not significantly decreased), and were subsequently treated with erbium:YAG laser. All patients included in this study had a minimum 4-week follow-up or until their wound healed.

**Financial Disclosure:** None reported.

**Conflict of Interest**: L.A.L. discloses consultant/advisory roles with Boehringer and MEDLINE, as well as research funding from Osiris, Integra, Cardinal, Medimmune, and EO2. None reported for the remaining authors.

Address correspondence to: Lawrence A. Lavery, DPM, MPH, Department of Plastic Surgery, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-8560.

*E-mail address:* matthewj.johnson@utsouthwestern.edu (M.J. Johnson).

1067-2516/$ - see front matter © 2019 by the American College of Foot and Ankle Surgeons. All rights reserved.
https://doi.org/10.1053/j.jfas.2019.07.023

Demographic data were collected along with a medical and social history, wound characteristics, results of serum laboratory studies, clinical outcomes, and peripheral vascular status. The ulcer history included etiology, location, previous treatment, and duration. Standard wound care consisted of sharp debridement using a curette or scalpel at weekly clinic visits to provide a bleeding wound base and margins. Off-loading was provided based on the location of the ulcer and the patient's postural stability and included total contact casts, removable cast boots, or flat, stiff-soled sandal. Standard dressings included cadexomer iodine 40 g/1.4 oz gel (Smith & Nephew, London, UK) and gauze dressing applied once a day. Standard wound care did not change during the course of the study, with the exception of laser debridement in substitution for sharp debridement.

The total surface area of each wound was calculated by multiplying the length and width and recorded in $cm^2$. Foot wounds were defined as full-thickness lesions involving any portion of the foot or ankle as previously described in the University of Texas Wound Classification System (19). Sensory neuropathy was defined, as stated by the International Working Group on the Diabetic Foot, if 2 of 3 sites tested on the foot using 10-g monofilament were not perceived or if there was abnormal vibration with a 127 HTZ tuning fork (20). Peripheral artery disease was defined as an ankle:arm systolic blood pressure ratio of <0.90 (21).

The data were compiled by using SPSS software version 24 for Macintosh (IBM, Armonk, NY). The percent wound area reduction (PWAR) was calculated at initiation of laser therapy and after 4 weeks of laser treatment. PWAR was calculated by subtracting the most recent wound measurement (no. 2) from the initial wound measurement (no. 1) and then dividing by the no. 1 measurement and multiplying by 100. The laser settings (Joule ProFractional 2940 nm; Sciton, Palo Alto, CA) were the same for all treatments. The ablation depth was 100 μm/25 J/$cm^2$ with level 1 coagulation mode (50 μm), fractionated treatment was 100 μm at 22% density with a spot size of 430 μm, and the total laser debridement time per wound, per clinic visit, was 30 seconds. A paired $t$ test was used to compare the change in wound area reduction (WAR) before and after the initiation of laser therapy, and a $\chi^2$ test was used to compare the proportion of patients with 50% WARbefore and after initiation of laser therapy with an $\alpha$ of .05.

## Results

The Table provides patient demographics and characteristics for the study population. No statistically significant descriptive data for this study population were observed ($p > .05$). During the 6-month treatment period, 35 patients with 56 wounds received laser debridement. There were 18 patients with 22 wounds that met inclusion criteria and were analyzed for this study. The remaining 17 patients with 34 wounds were excluded: 5 patients had venous stasis (14 wounds), 2 patients had no history of diabetes (2 wounds), 3 patients underwent surgical intervention before completing follow-up (2 bone resections with primary wound closure, 1 toe amputation), 6 patients did not have 4-week wound measurements before the initiation of laser therapy (14 wounds), and 1 patient (1 wound) received an advanced wound product before completing follow-up. During the 4-week period before the initiation of laser therapy, the average PWAR was −32.1% (median PWAR 27%). Four weeks after the initiation of treatment with the erbium:YAG laser, the mean PWAR was 63.5% (median PWAR 74.5%).

**Table**
Descriptive Data (N = 22 wounds in 18 patients)

| | Total | ≥50% Wound Area Reduction (n = 16) | <50% Wound Area Reduction (n = 5) | $p$ Value |
|---|---|---|---|---|
| Age, yr, mean (SD) | 60.9 (13.7) | 62.4 (13.6) | 60.3 (15.1) | .76 |
| Male sex, n (%) | 14 (73.6) | 13 (81.3) | 3 (50) | .15 |
| Race, n (%) | | | | |
| White | 17 (77.3) | 12 (75.0) | 5 (83.3) | .69 |
| African decent | 3 (13.6) | 2 (12.5) | 1 (16.7) | .80 |
| Hispanic | 2 (9.1) | 2 (12.5) | 0 (0.0) | .37 |
| Body mass index, n (%) | 31.2 (6.8) | 31.2 (7.7) | 30.7 (4.3) | .88 |
| Glycated hemoglobin, mean (SD), % | 6.94 (1.4) | 6.7 (1.2) | 7.3 (2.0) | .40 |
| eGFR, mL/min/1.73 $m^2$, mean (SD) | 40.2 (20.9) | 41.8 (19.6) | 39.8 (27.6) | .85 |
| Diabetes mellitus type 2, n (%) | 18 (81.8) | 13 (81.3) | 6 (100) | .27 |
| Sensory neuropathy, n (%) | 22 (100) | 16 (100) | 6 (100) | >.999 |
| Ankle-brachial index, mean (SD) | 1.2 (0.3) | 1.2 (0.4) | 1.4 (0.1) | .25 |

Based on the use of a paired $t$ test, the 4-week post–laser treatment PWAR was significantly greater than before laser treatment (95% confidence interval −152.7 to −41.2; $p = .002$). Results are summarized in the Fig. Sixteen (72.7%) of 22 wounds achieved >50% WAR at 4 weeks. Eleven (50%) of 22 wounds were completely healed at or before 12 weeks. None of the 6 wounds with <50% WAR at 4 weeks were healed by 12 weeks.

## Discussion

The purpose of this study was to investigate the effectiveness of high-intensity erbium:YAG laser in DFUs that had failed to respond to the standard of care for DFU. Wounds treated with the erbium:YAG laser showed significant WAR in 4 weeks of treatment. The findings of the current study are similar to the findings of 2 randomized clinical trials (RCTs) that used laser therapy for DFUs. However, there are important differences. Ebid et al (16) and Basalamuh et al (17) used the neodymium (Nd):YAG laser with 3 treatments per week. The Nd:YAG laser system is nonablative and has more of a coagulative wavelength. We used the erbium:YAG laser, which is highly ablative, and treatment was provided once per week.

RCTs by Ebid et al (16) and Basalamuh et al (17) report improved healing with laser therapy in patients with DFUs. Both studies were 8 weeks in duration, and the primary endpoint was WAR. Ebid et al (16) randomized 20 patients to receive “standard medical therapy” versus 20 patients to receive Nd:YAG laser treatments 3 times per week. “Standard medical therapy” was defined as hypoglycemic medications, systemic antibiotics according to culture tests, debridement for removal of necrotic tissues and foreign bodies when needed, irrigation of the wound with normal saline solution twice daily, and dressings with sterile gauze. The laser was set at 4 J/$cm^2$; if a wound was 10 $cm^2$, the amount of energy applied to the wound was 40 J per treatment. WAR in the laser treatment group was significantly greater than WAR in the standard wound therapy group. At baseline, the average wound size in the laser treatment group versus control group was 8.10 $cm^2$ versus 8.75 $cm^2$, respectively. After 4 weeks of therapy, the average PWAR was 50% (4.05 $cm^2$) and 7.9% (7.75 $cm^2$) respectively. The number of healed wounds was not reported. Basalamuh et al (17) randomized 21 patients to receive sham laser therapy and 22 patients to receive Nd:YAG laser therapy 3 times per week at 230 to 250 J total. After 4 weeks. the PWAR was 0.72% for the placebo group and 31% for the laser treatment group ($p < .05$).

We chose to identify wound healing at 4 weeks because this has been described as a robust predictor of healing in 12 to 20 weeks and it allowed us to compare treatment progress before and after the initiation of laser therapy (23–26). Margolis et al (23) were the first to show this surrogate marker discriminated between wounds that healed and wounds that did not heal by the 12th week of care. Sheehan et al (24) assessed the ability of the 4-week healing rate to predict complete healing a 12-week period in a post-hoc analysis of a prospective multicenter trial of 203 patients with DFUs and found that the midpoint between the PWAR from baseline at 4 weeks in patients who healed was 53%. The sensitivity, specificity, and negative and positive predictive values of this cutoff point to predict healing by 12 weeks were 91%, 58%, 91%, and 58%, respectively. In an RCT of 97 patients with DFUs, Lavery et al (25) reported that among patients in the active treatment arm, 62% had >50% WAR and 62% of patients healed. In a retrospective cohort study of 704 patients, Coerper et al (26) reported that ulcers with >50% versus <50% PWAR by 4 weeks had a significantly higher probability of healing by 12 weeks (52.3% versus 18.4%, $p = .0001$).

The mechanism of action of the erbium:YAG laser is not completely understood, but it appears to be more than just standard sharp debridement. Results from in vitro studies suggest that laser photostimulation affects many molecular alterations, including increased ATP synthesis,

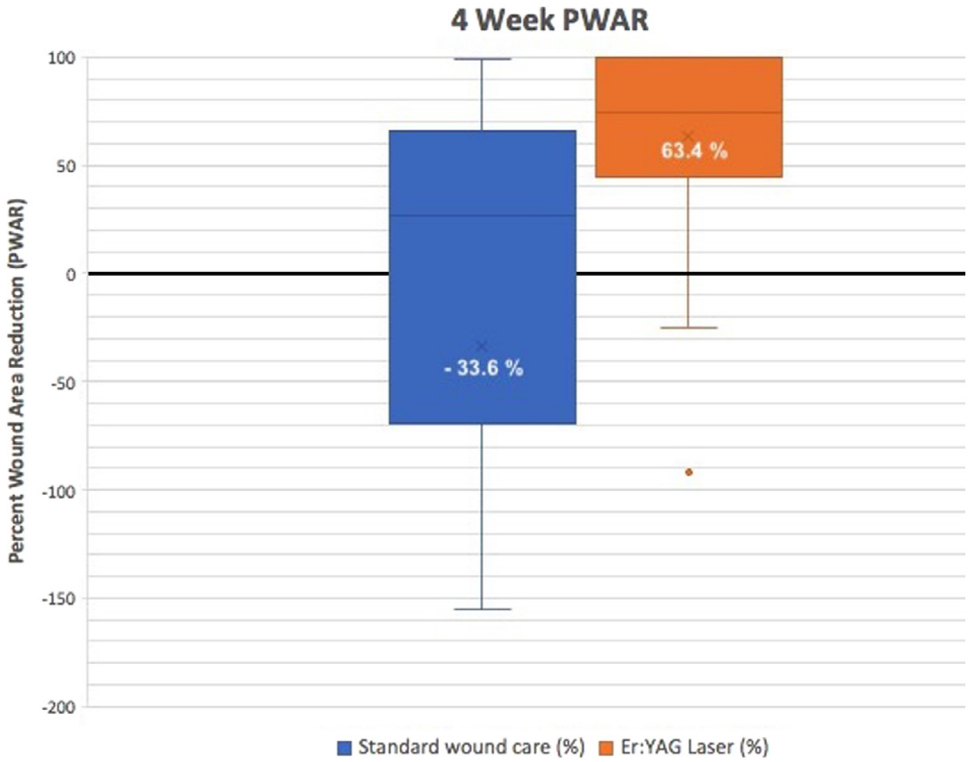


**Fig.** Four-week percent wound area reduction—separate.

nucleic acid production, increased cell division, fibroblastic proliferation, and collagen synthesis. All of these factors may contribute to an accelerated healing process (14,15). Ebid et al (16) stated that laser light stimulates increased production of ATP from ADP molecules in the mitochondria of cells; however, the molecular pathway underlying laser light–stimulated ATP production has not yet been identified (16,22). Regrading the laser used in the 2 published RCTs (Nd:YAG), Nd does not have ablative properties and erbium is highly ablative, and Nd does not remove tissue.

There are important limitations of this study. The most obvious limitation of this study is its retrospective nature, leading to potential measurement and selection bias. There is the potential for varying operational definitions of disease states and outcomes used by different clinicians. However, the strength of the study is that the data were from a wound center with standardized procedures, testing, and operational definitions. This cohort represents the "real world" type of patients who seek treatment at wound centers and not patients who are enrolled in trials with strict inclusion and exclusion criteria. Although not all patients were treated with the same frequency, most were treated on a weekly basis. This is in sharp contrast to RCTs that provide laser treatment 3 times a week. We compared the PWAR before and after laser therapy, and other variables such as the type of dressing and off-loading were consistent. We acknowledge that the most rigorous scientific method is to compare the proportion of DFUs that healed in a prospective randomized trial to eliminate selection bias. Finally, high-intensity erbium:YAG laser equipment is expensive and consequently may not be widely available at the current time.

In conclusion, the results of this study demonstrate promising outcomes in the treatment of patients with DFUs. However, further investigation in a prospective RCT is required to confirm our findings. At the current time, the ideal dosing parameters or frequency of therapy remains unknown. The 2 published RCTs provided treatment 3 times a week with a different laser application; however, we found significant improvement with therapy provided only once a week. Future studies should strive to further understand the mechanism of action, identify any device-related adverse events, and provide guidance on which wounds are ideally treated with high-intensity erbium:YAG laser.

## References

1. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care 1998;21:822–827.
2. Driver VR, Lavery LA, Reyzelman AM, Dutra TG, Dove CR, Kotsis SV, Kim HM, Chung KC. A clinical trial of Integra Template for diabetic foot ulcer treatment. Wound Repair Regen 2015;23:891–900.
3. Smiell JM, Wieman TJ, Steed DL, Perry BH, Sampson AR, Schwab BH. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. Wound Repair Regen 1999;7:335–346.
4. Lavery LA, Fulmer J, Shebetka KA, Regulski M, Vayser D, Fried D, Kashefsky H, Owings TM, Nadarajah J; Grafix Diabetic Foot Ulcer Study Group. The efficacy and safety of Grafix((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J 2014;11:554–560.
5. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for Medicare and private insurers. Diabetes Care 2014;37:651–658.
6. Wukich DK, Raspovic KM. Assessing health-related quality of life in patients with diabetic foot disease: why is it important and how can we improve? The 2017 Roger E. Pecoraro Award Lecture. Diabetes Care 2018;41:391–397.
7. Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, Romanelli M, Stacey MC, Teot L, Vanscheidt W. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen 2003:(suppl 1):S1–S28.
8. Elraiyah T, Domecq JP, Prutsky G, Tsapas A, Nabhan M, Frykberg RG, Hasan R, Firwana B, Prokop LJ, Murad MH. A systematic review and meta-analysis of debridement methods for chronic diabetic foot ulcers. J Vasc Surg 2016;63 (suppl). 37S–45S e1–e2.
9. Braun L, Kim PJ, Margolis D, Peters EJ, Lavery LA, Wound Healing S. What's new in the literature: an update of new research since the original WHS diabetic foot ulcer guidelines in 2006. Wound Repair Regen 2014;22:594–604.

10. Phillips TJ, Morton LM, Uebelhoer NS, Dover JS. Ablative fractional carbon dioxide laser in the treatment of chronic, posttraumatic, lower-extremity ulcers in elderly patients. JAMA Dermatol 2015;151:868–871.
11. Krakowski AC, Diaz L, Admani S, Uebelhoer NS, Shumaker PR. Healing of chronic wounds with adjunctive ablative fractional laser resurfacing in two pediatric patients. Lasers Surg Med 2016;48:166–169.
12. Mahran HG, Faruk EM, El Sawy NA, Shousha TM, Abdelgalil AA, Alhasan H, Alshehri MA. Pulsed high intensity laser versus low intensity laser on healing of full thickness wound in diabetic rats. Int J Pharma Bio Sci 2017;8:874–888.
13. Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008;16:19–22.
14. Yaakobi T, Maltz L, Oron U. Promotion of bone repair in the cortical bone of the tibia in rats by low energy laser (He-Ne) irradiation. Calc Tiss Intl 1996;59:297–300.
15. Enwemeka CS. Ultrastructural morphometry of membrane-bound intracytoplasmic collagen fibrils in tendon fibroblasts exposed to He:Ne laser beam. Tiss Cell 1992;24:511–523.
16. Ebid AA, El-Kafy EM, Alayat MS. Effect of pulsed Nd:YAG laser in the treatment of neuropathic foot ulcers in children with spina bifida: a randomized controlled study. Photomed Laser Surg 2013;31:565–570.
17. Basalamah MA, Abdelgayed AE, Thabet AA, Abdel-Kafy EM. Effect of pulsed high intensity laser in treatment of diabetic foot ulcer: a randomized controlled study. Jokull 2013;63:171–179.
18. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015;38(suppl):S8–S16.
19. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998;21:855–859.
20. International Working Group on the Diabetic Foot. Prevention and Management of Foot Problems in Diabetes: A Summary Guidance for Daily Practice 2015; Based on the IWGDF Guidance documents. Available at: http://www.iwgdf.org/files/2015/website_summary.pdf. Accessed February 11, 2019.
21. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45(suppl S):S5–S67.
22. Manteĭfel' VM, Karu Ti. Increase of number of contacts of endoplasmic reticulum with mitochondria and plasma membrane in yeast cells stimulated to division with He-Ne laser light. Tsitologia 2004;46. 498–450.
23. 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.
24. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003;26:1879–1882.
25. Lavery LA, Fulmer J, Shebetka KA, Regulski M, Vayser D, Fried D, Kashefsky H, Owings TM, Nadarajah J; Grafix Diabetic Foot Ulcer Study Group. The efficacy and safety of Grafix(®) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J 2014;11:554–560.
26. Coerper S, Beckert S, Kuper MA, Jekov M, Konigsrainer A. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single-center cohort of 704 diabetic patients. J Diab Compl 2009;23:49–53.