

ORIGINAL CONTRIBUTION

## Topical Hyperbaric Oxygen and Low Energy Laser Therapy for Chronic Diabetic Foot Ulcers Resistant to Conventional Treatment

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*Chronic foot ulcers are common in long-standing diabetes, may herald severe complications and are often resistant to therapy. To evaluate the effects of adjunctive topical hyperbaric oxygen treatment (THBO) and low energy laser (LEL) irradiation on ulcer healing, a 100 consecutive patients with chronic diabetic foot ulcers (DFU) refractory to 4.5 ± 1.2 months of comprehensive treatment, were enrolled in a prospective open study. While conventional treatment was continued as necessary, THBO was administered by pumping 100 percent oxygen into a disposable sealed polyethylene hyperbaric chamber (150 min x 2 to 3/wk at up to 1.04 atm). Helium-neon LEL irradiation was given concurrently using a Unilaser Scan Unit at 4J/cm<sup>2</sup> for 20 min. Some patients continued THBO at home or their treatment was confined to THBO at home. Patients were monitored every two weeks revealing 81 percent cure after 25 ± 13 treatments over 3.2 ± 1.7 months. On follow-up (median 18 months), only 3/81 (4 percent) had reulceration, which responded to THBO/LEL retreatment. Non-responders had significantly lower ankle brachial indices (ABI) than patients whose ulcers were healed (0.55 vs. 0.78, p < 0.01) and ultimately required amputation. Patient compliance was full and no adverse events occurred. In conclusion, although the study was open and uncontrolled, an 81 percent healing of DFU in patients who previously did not respond to a comprehensive treatment program, constitutes an intriguing preliminary result. Thus, THBO/LEL therapy may be a safe, simple, and inexpensive early adjunctive treatment for patients with chronic diabetic foot ulcers. Our findings should prompt its evaluation by large randomized controlled trials.*

Chronic foot ulcers are a common complication of long-standing diabetes, affecting up to 20 percent of patients. Their treatment is difficult, prolonged, and often unsuccessful, and the patients are prone to serious complications. Systemic hyperbaric oxygen (HBO<sup>c</sup>) therapy is used

as an adjunctive method to treat various difficult wounds including diabetic foot ulcers (DFU), even though its effectiveness is still controversial [1]. A recent randomized study showed that the addition of systemic HBO treatment compared to conventional treatment in diabetic patients

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<sup>c</sup> Abbreviations: HBO, hyperbaric oxygen; DFU, diabetic foot ulcers; THBO, topical HBO; LEL, low energy laser; ABI, ankle-to-brachial pressures.

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with severe foot ulcers, decreased the need for major amputation by almost four-fold (relative risk 0.26) [2]. However, availability and cost somewhat limit the usefulness of this treatment modality. Interestingly, topical HBO (THBO) treatment for DFU and various chronic ulcers also showed promising results in a few uncontrolled studies [3-5] but was largely abandoned following a prospective controlled study which failed to demonstrate any benefit. This study was too short, however, for meaningful conclusions and lasted only 14 days [6].

The technology of low energy laser (LEL) was introduced into clinical medicine more than three decades ago but has not received much attention. Nevertheless, LEL has a stimulating effect on cell mitosis [7], keratinocyte migration and proliferation [8, 9], and on cytokine production [10, 11] and may lead to increased dermal angiogenesis [12]. Animal experiments have suggested an enhancing effect of LEL on wound healing, and this was supported by a few preliminary clinical studies [13-15]. Investigations using both THBO and LEL were not previously reported to our knowledge, yet a synergistic effect of combined therapy is possible and our preliminary results were encouraging [16]. In this study we report our experience with a combination of THBO and LEL in the treatment of chronic diabetic foot ulcers when conventional treatment failed.

## PATIENTS AND METHODS

Since 1995, diabetic patients who had chronic foot ulcers were referred to us by general practitioners or by other clinics (Vascular Surgery, diabetes) of the hospital. A complete history, physical examination, and appropriate blood tests were obtained, as well as foot X-ray and ankle blood pressure determination to calculate ratio of ankle to brachial pressures (ABI).

All patients underwent a neurologic exam. Biopsies and cultures were obtained as needed but not routinely, and plethysmography to assess venous flow was also performed when clinically indicated. Conventional treatment was administered by our group, which included infectious diseases, endocrinology, vascular surgery, and orthopedic consultants. We aimed at optimal diabetes and risk factor control and administered recommendations for non-weight bearing and special shoes, repeated debridement and local treatment of the ulcers, and prolonged use of broad spectrum antibiotics [17]. Therapies did not include compression, Regranex (PDGF) or recombinant skin. The patients were frequently seen, mostly on an out-patient basis. In addition, the team was easily accessible to the patients, who could make an appointment and be examined within a short time. The first 100 consecutive patients without gangrene whose ulcers remained refractory to at least 14 weeks (median 17 weeks) of comprehensive conventional treatment by the team were referred for THBO and LEL therapy and are the subject of this study (see under Results). THBO was administered by pumping 100 percent humidified oxygen into a hyperbaric chamber made of a 100 x 60 cm disposable polyethylene bag placed over the leg and sealed above the knee by an elastic bandage (150 min x 2 to 3/week, up to 1.04 atm). The same apparatus was used for ambulatory treatment with a regular oxygen concentrator as an oxygen source. Helium-neon LEL irradiation was administered concurrently using a Uni-laser Scan 60 (Elettronica, Pagany, Italy). The unit has an automatic scanner and provided low sources of laser (wavelength and power of 632.8 nm/5mW and 904 nm/60W, for He-Ne and infrared laser, respectively). During each treatment a dose of 4 J/cm<sup>2</sup> was irradiated to the surface of the ulcer, for 20 minutes. Over the whole period, conventional treatment was

continued as necessary. Patients were monitored at least once every two weeks and the appearance of the ulcer recorded by the same observer. The primary end point was ulcer healing, defined as complete closure of the ulcer with normal skin or scar formation. Following ulcer healing, patient follow-up was continued at a lower frequency but at least once every three months.

## RESULTS

Over the period of the study, 347 patients with diabetic foot ulcers were referred to us. In 233 patients, cure of the ulcer was achieved by conventional therapy (67 percent), and 14 were lost to follow up. The remaining first 100 patients whose ulcers did not heal with prolonged established therapy over  $4.5 \pm 1.2$  months (median 17 weeks, range 14 to 24 weeks) are the subject of the present study. All 100 patients had longstanding type 2 diabetes (median 11 years). Their ages were  $64 \pm 10$  years (mean  $\pm$  SD), 51 percent were males. Most patients' diabetes was treated with oral agents, and only a small minority were treated with insulin. Diabetes was poorly controlled in most patients at pre-

sentation ( $\text{Hb A}_{1\text{C}} > 7.5$  percent) and also notable was a high frequency of other microvascular complications such as diabetic retinopathy and nephropathy. All patients (100 percent) had diabetic peripheral neuropathy on presentation. The foot ulcers were present for  $7 \pm 5$  months (range 2 to 17 months) before referral. Most patients were treated with both THBO and LEL therapy, and the mean duration of treatment was  $3.2 \pm 1.7$  months. The treatment characteristics and results are given in Table 1. Eighty-one patients (81 percent) were cured. On a median follow-up of 18 months (range 12 to 39 months), reulceration occurred in only 4 percent (3/81) and early retreatment with THBO/LEL led again to ulcer healing in all cases. Amputations were limited to those patients who failed treatment (19/19), and these patients had lower ABI than those who responded to THBO/LEL treatment ( $0.55 \pm 0.14$  vs.  $0.78 \pm 0.18$ ,  $p < 0.01$ ), but no other significant differences were found (not shown). No adverse reactions were noted and notably, no patient was lost to follow up. Patient compliance was maximal (100 percent). Part of this adherence can no doubt be attributed to patient satisfaction. Patients often

**Table 1. Treatment of 100 diabetic patients with chronic foot ulcers who failed conventional treatment by topical hyperbaric oxygen (THBO) and low energy laser (LEL) therapy.**

Ulcer duration before referral (months)	$7 \pm 5$
Conventional treatment duration (months)	$4.5 \pm 1.2$
THBO & LEL treatment:	
Duration (months)	$3.2 \pm 1.7$
Number of treatments	$25 \pm 13$
Treatment group and results (cured/total in group):	
a. In hospital THBO & LEL	53/64 (83%)
b. In hospital THBO & LEL followed by THBO at home	21/25 (84%)
c. THBO alone, at home	7/11 (64%) <sup>a</sup>
Total cured <sup>b</sup>	81/100 (81%)
Recurrent ulceration <sup>c</sup>	3/81 (4%)

<sup>a</sup> Nineteen patients failed and ultimately required amputation

<sup>b</sup> Differences between a and b and between a + b and c are not statistically significant.

<sup>c</sup> Over a follow-up period of 18 months (median)

expressed their satisfaction with the program, enthusiasm with the results (not quantitated), and stressed their wish to remain on the study and continue THBO treatment.

## DISCUSSION

Diabetic foot ulcers are notoriously prone to complications and resistant to therapy [17]. Even with "best" conventional treatment which includes improved glycemic control, decreased weight bearing, local treatment of the ulcers and systemic antibiotics, many ulcers remain unhealed. Our combined conventional therapy achieved primary healing in 67 percent of the patients only. This is consistent with the results of other centers which reported success in 182/281 Swedish patients (65 percent) [18] and in 55 to 63 percent of the patients in two additional recent series [19, 20]. This result, therefore, supports the contention that the non-responding patients referred for THBO/LEL therapy were truly resistant or refractory to prolonged "conventional" treatment.

Our approach, of adding THBO and LEL therapy to the multi-disciplinary conventional modalities is based on previous biological and early clinical observations [3-15]. It resulted in a further 80 percent of the patients with chronic diabetic foot ulcers being cured. The results are even more striking considering the fact that prior prolonged conventional therapy for about four months failed in these patients. Nevertheless, subsequently, about 12 weeks only of adjunctive THBO/LEL therapy were sufficient to obtain ulcer cure in most of the patients (Table 1). This suggests that the introduction of adjunctive THBO/LEL therapy at an early, initial stage of DFU treatment, might be beneficial. Using this approach for both naive and treatment-resistant DFU might also be cost effective, since both modalities do not

require expensive equipment or personnel. Furthermore, THBO can be continued at the patient's home, apparently with no significant loss of efficacy (Table 1). One rationale of treatment of diabetic foot ulcer with THBO is to use the lethal effect of oxygen on the anaerobic bacteria present in the diabetic ulcer. Indeed we observed that after a few treatments the foul odor of anaerobic bacteria disappeared from the ulcers. Although the identification of microbiological isolates from foot ulcers was not routinely attempted in this study, data from other studies show that DFU yield mixed cultures of microorganisms [8, 21]. Staphylococci (both *Staphylococcus aureus* and coagulase-negative *Staphylococcus*) predominate, but other Gram-positive, Gram-negative and anaerobic bacteria are often found. Infections are usually polymicrobial and curettage of the base of foot ulcers or deep tissue cultures are most reliable for identifying true pathogens [22, 23] as opposed to simple cultures of the foot ulcer. We used prolonged courses of broad spectrum beta-lactam antibiotics or a combination of antibiotics active against facultatively aerobic cocci and bacilli as well as anaerobes, administered early as part of the standard therapy. Nevertheless a sizeable proportion (one third) of the patients' ulcers remained refractory, but later showed a response rate of about 80 percent to THBO/LEL treatments.

HBO, even at low pressures as used by us, has an additional stimulatory effect on wound healing and its combination with LEL may have an additive effect: in four patients who developed a new ulcer while on ambulatory THBO therapy, immediate LEL application cured their lesion very quickly, again suggesting that early THBO/LEL intervention might further improve the results. This is supported by a recent randomized controlled trial of LEL vs. sham irradiation in 30 patients with DFU or gangrene, which found a

significant rise in skin temperature in the LEL group, reflecting improved skin microcirculation [24]. This finding may underlie the remarkably low rate of ulcer recurrence in our series, as opposed to a reported recurrence rate of more than a third of patients within one year [25]. This is an unexpected observation which merits further confirmation.

Several limitations of our study should be noted. Our study was open, unblinded, and our patients served as their own controls in the period of "conventional" therapy. This is problematic and open to criticism that the observed high rate of ulcer cure is merely the result of further prolonging conventional treatment. However, after  $4.5 \pm 1.2$  months, we felt that our patients' foot ulcers were truly refractory to established treatments and this is line with historical controls [18-20]. It is also not entirely clear which of the two treatments, or their combined use, was the effective modality. The differences in therapeutic effects between the two groups (THBO/LEL vs. THBO alone) were insignificant (Table 1). On the other hand, the high safety profile of both treatments suggest that until further data are available, concurrent treatment should be attempted whenever possible.

We conclude that in conjunction with standard treatments, the added application of THBO/LEL may have a true beneficial effect on the natural history of chronic therapy-resistant diabetic foot ulcers. This is also reflected in the low prevalence of reulceration. THBO/LEL treatment is simple, inexpensive, and can easily be adopted to primary care settings. Thus, our main conclusion is that these preliminary results should resurrect interest in adjunctive THBO/LEL therapy for chronic foot ulcers in diabetic patients, and should lead to large-scale randomized controlled trials in the future.

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