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European Journal of Internal Medicine 17 (2006) 272 – 275

EUROPEAN JOURNAL OF INTERNAL MEDICINE

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Original article

Topical hyperbaric oxygen and low-energy laser for the treatment of chronic ulcers

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Received 15 August 2005; received in revised form 2 October 2005; accepted 17 November 2005

Abstract

Background: Diabetic foot ulcers (DFU) and chronic venous ulcers (CVU) are persistent cutaneous lesions that are difficult to treat and heal. Topical hyperbaric oxygen (THO) and low-energy laser (LEL) are therapies that have been employed separately for ulcer treatment, but their concomitant use has not been investigated.
Methods: In this unblinded, open-label non-randomized trial, we treated 374 consecutive patients with treatment-refractory chronic ulcers (218 patients with DFU and 156 individuals with CVU) with a combination of THO and LEL. THO was administered by pumping 100% oxygen into a disposable, sealed polyethylene chamber for 2 h, two to three times weekly. LEL was administered concurrently using a helium–neon laser at 4 J/cm^2 for 20 min.
Results: Complete ulcer closure was obtained in 78% of patients in each group (170 patients with DFU and 127 patients with CVU). Treatment failure resulting in amputation in DFU was seen in 48 patients (22%); non-closure of ulcers within 18 months in individuals with CVU was seen in 29 (22%). The length of therapy was also similar in the two groups (3.7±3 versus 4.1±3 months in DFU and CVU cohorts, respectively). However, the number of treatments required to affect healing was greater in the CVU group than among the DFU patients (40±25 versus 31.4±20 treatments).
Conclusion: THO and LEL therapies are safe, effective, simple and inexpensive therapies for DFU and CVU. Confirmation must await the performance of double-blind, randomized, controlled trials currently under way.

Keywords: Chronic venous ulcer; Diabetic foot ulcer; Topical hyperbaric oxygen; Low-energy laser

1. Introduction

Diabetic foot ulcers (DFU) and chronic venous ulcers (CVU) are cutaneous lesions that are difficult to treat and heal. Conventional therapies, including local treatment/debridement and antibiotics, are frequently ineffective. Even when successful, these treatments result in wound healing that occurs slowly and with a great deal of pain and disability.

Topical hyperbaric oxygen (THO) therapy is a technique that was used to treat diabetic foot ulcers in a few uncontrolled clinical trials in the 1960s and 1970s [1–3]. However, this therapy was almost completely neglected in the western world, especially after Leslie et al. published their unfavorable experience with THO in patients with DFU [4].

Despite this unfavorable report, interest in THO continued among a few groups [5–7] and, recently, interest in this modality has increased. For example, Sen et al. published their treatment experience with THO and the possible role of topical oxygen in the mechanism of wound healing [8,9]. In addition, THO administered by inflatable "oxygen boots" was approved by the Food and Drug Administration (FDA) for the treatment of DFU and it is currently used by many clinics around the U.S.

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0953-6205/$ - see front matter
doi:10.1016/j.ejim.2005.11.028

The technology of low-energy laser (LEL) was introduced into clinical medicine more than three decades ago but had received little attention [10]. LEL has a stimulating effect on cell mitosis [11], keratinocyte migration [12], proliferation [13] and cytokine production [14], and it may lead to increased dermal angiogenesis [15]. Animal experiments have suggested an enhancing effect of LEL on wound healing and this was supported by a few preliminary clinical studies [16–21].

Investigations using both THO and LEL have not been previously reported, yet a synergistic effect is possible and our preliminary results were encouraging. In this observational prospective study, we report our experience with a combination of these modalities in the treatment of patients with chronic ulcers for whom conventional treatment failed.

2. Patients and methods

2.1. Patients

Patients with chronic (more than a month) DFU or CVU who were referred to us by general practitioners, vascular and orthopedic surgeons, and dermatologists from 2000 to 2004 were included in this study. All patients underwent an evaluation that included a complete history, physical and neurological examinations, and appropriate blood tests. In addition, X-rays of the affected area(s) were obtained and ankle blood pressures were determined in order to calculate the ankle-to-brachial ratio (ABI). Patients with an ABI below 0.3 or with black, gangrenous ulcers were excluded from the study. Cultures were obtained as needed and plethysmography or Doppler examinations were performed when clinically indicated.

Conventional treatment was administrated by our group, which included specialists in infectious diseases, endocrinology, vascular surgery and orthopedics. This included topical treatment and pressure bandages in the case of CVU, and debridement, oral antibiotics according to wound cultures and weight off-loading. In the case of DFU, this was combined with local ulcer care (with various creams, ointments or saline). We aimed at optimal diabetes and risk factor control and administrated recommendations for non-weight-bearing and orthopedic shoes when needed.

The patients were seen twice weekly at our hospital clinic. Patients who had ambulatory difficulties were treated at home and seen every week or every other week. The study was approved by the hospital Helsinki committee and all patients gave informed consent to participate in the treatment protocol.

2.2. Methods

THO was administered by pumping 100% oxygen into a hyperbaric chamber made of a 100×60 cm disposable polyethylene bag placed over the leg and sealed above the knee with an elastic bandage. Treatment was given for 120 min, two to three times weekly (pressure within the bag was measured at 1.04 atm). The same apparatus was used for ambulatory treatment with a regular oxygen concentrator as an oxygen source.

LEL was administered using one of the following two helium–neon devices: (1) the Unilaser Scan 60 (Elettronica, Pagany, Italy), which has an automatic scanner and provides a low source of laser energy: wavelength and power of 632.8 nm, 5 mW and 904 nm, 60 W for He–Ne and infrared laser, respectively; or (2) Terraquant Israel. This device also has a He–Ne source of light and infrared energy (wavelength 600–700 nm, He–Ne energy 60–90 mW). During each treatment, a dose of 4 J/cm^2 was irradiated to the surface of the ulcer with one of the above devices (randomly assigned) for 10 min by Terraquant or for 20 min by the Unilaser Scan. Conventional treatment was continued during the treatment period.

Patients were monitored at least once weekly and the appearance of the ulcer was recorded by the same observer (ZL). The primary endpoint was ulcer healing defined as complete closure of the ulcer. Failure was defined as amputation in the case of DFU or non-cure in the case of CVU after 15 months of treatment.

3. Results

Overall, we treated 374 patients with chronic, non-healing ulcers during the study period. Of these, 218 patients had DFU and 156 had CVU. In general, the DFU group was older (mean age 67.7 versus 60.2 years in the CVU cohort), but the mean duration of ulcers before the start of treatment was similar in both groups (2.9 ± 2.0 versus 3.1 ± 2 months in the DFU and CVU groups, respectively). Mean glycosylated hemoglobin (Hgb A1C) level was 8.2 ± 2.3 in the DFU group, and the distribution of ulcers in this cohort was 46 with grade I, 102 with grade II, 45 with

Table 1
Patient characteristics and results of therapy

Patient characteristics	DFU number (%)	CVU number (%)
Men	118 (54)	70 (44)
Women	100 (46)	86 (56)
Age (years)	67.7	60.2
Non-insulin therapy	125 (57)	N/A
Peripheral neuropathy	200 (92)	N/A
Peripheral vascular disease	113 (52)	N/A
Ulcer duration (months)[a]	2.9 ± 2	3.1 ± 2
Results of therapy		
Length of therapy (months)	3.7 ± 3	4.1 ± 2.5
Mean number of treatments	31.4 ± 20	40 ± 25
Ulcer healing	170 (78)	127 (78)
Treatment failure	48 (22)	29 (22)

N/A=not applicable.
[a] Prior to treatment.

grade III and 25 with grade IV ulcers according to Wagner's scale [23].

The length of therapy was similar in both groups (3.7±3 versus 4.1±3 months in DFU and CVU cohorts, respectively). However, the number of treatments required to affect healing was greater in the CVU group than in the DFU patients (40±25 versus 31.4±20 treatments). An analgesic effect was seen in a special subgroup of patients with small necrotic areas on their feet who were not considered to be surgical candidates. Within 10–20 sessions, pain disappeared and necrotic areas were replaced by normal tissue.

Complete ulcer closure was obtained in 78% of patients in each group (170 patients with DFU and 127 patients with CVU). We used laser therapy alone in a group of 20 patients with varicose vein ulcers in whom there was no evidence of infection. In this selected group, all were cured within 3 months. Treatment failure was seen in 48 patients (22%) with DFU and in 29 (22%) with CVU.

Patient demographics and treatment results are summarized in Table 1.

4. Discussion

DFU and CVU arise as a result of different pathophysiologic mechanisms but share many clinical features. These features include their chronicity, morbidity and similarity in response to conservative treatment. In this prospective observational study, two modalities–THO and LEL–were used in addition to conventional therapy.

The rationale for THO is to deliver oxygen directly to the open wound, which results in a number of clinical benefits. First, oxygen has a direct effect on anaerobic bacteria, frequent pathogens in diabetic ulcers. This manifested itself clinically by the rapid disappearance of the typical foul smell of the anaerobic organisms within a few days. Second, oxygen has a proliferative effect and this could be seen in the rapidly growing epithelium at the edge of the ulcers and the reduction in oozing and skin maceration. Finally, topical oxygen has an apparent analgesic effect, which was also noted within a few days of treatment initiation.

The use of plastic inflatable "oxygen boots" has many advantages. First, treatment is simple and does not require specialized training. Second, THO does not require a large amount of space; in fact, we were able to treat a number of patients in a single room (Fig. 1). Third, treatment can be done in an ambulatory setting or even in the patient's home. Finally, THO is very cheap. A large plastic bag costs only a few dollars and the oxygen costs only a few cents.

LEL also has many therapeutic and analgetic effects, as were readily apparent in our patients. In most of our patients, we combined THO and LEL in an attempt to obtain a synergistic therapeutic effect. It is our impression that this combination is more effective than either modality alone. Recently, Whelan et al. also described a synergistic effect from a combination of light energy and hyperbaric oxygen on wound healing [22].

Fig. 1. Patients receiving THO by oxygen boot.

In sum, our impression is that THO and LEL are promising techniques. Further confirmation, however, must await the performance of prospective, randomized, controlled studies, which are currently under way.

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