Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind, Randomized Controlled Clinical Trial

OBJECTIVE

Hyperbaric oxygen therapy (HBOT) is used for the treatment of chronic diabetic foot ulcers (DFUs). The controlled evidence for the efficacy of this treatment is limited. The goal of this study was to assess the efficacy of HBOT in reducing the need for major amputation and improving wound healing in patients with diabetes and chronic DFUs.

RESEARCH DESIGN AND METHODS

Patients with diabetes and foot lesions (Wagner grade 2–4) of at least 4 weeks duration participated in this study. In addition to comprehensive wound care, participants were randomly assigned to receive 30 daily sessions of 90 min of HBOT (breathing oxygen at 244 kPa) or sham (breathing air at 125 kPa). Patients, physicians, and researchers were blinded to group assignment. At 12 weeks post-randomization, the primary outcome was freedom from meeting the criteria for amputation as assessed by a vascular surgeon. Secondary outcomes were measures of wound healing.

RESULTS

One hundred fifty-seven patients were assessed for eligibility, with 107 randomly assigned and 103 available for end point adjudication. Criteria for major amputation were met in 13 of 54 patients in the sham group and 11 of 49 in the HBOT group (odds ratio 0.91 [95% CI 0.37, 2.28], \( P = 0.846 \)). Twelve (22%) patients in the sham group and 10 (20%) in the HBOT group were healed (0.90 [0.35, 2.31], \( P = 0.823 \)). All other indices of wound healing were also not statistically significantly different between groups.

CONCLUSIONS

HBOT does not offer an additional advantage to comprehensive wound care in reducing the indication for amputation or facilitating wound healing in patients with chronic DFUs.
Patients with diabetes are at high risk of lower-limb amputation because of the high incidence of chronic lower-extremity wounds or diabetic foot ulcers (DFUs) (1,2). Diabetic peripheral neuropathy with loss of protective sensation, peripheral artery disease, limited foot mobility, and foot deformities are the main etiologic reasons for difficulties in the prevention and treatment of DFUs (3). Nonhealing wounds pose a continuous risk of gangrene, local and systemic infection, sepsis, and death as well as a decline in quality of life (4). Defining the most effective treatment strategies is essential to reducing the burden of this disease (1). Hyperbaric oxygen therapy (HBOT) has been used as an adjuvant treatment for difficult-to-heal chronic diabetic foot wounds; however, most evidence for its efficacy is based on observational cohort studies or open-label randomized trials (5–9). HBOT requires significant patient time and financial commitment compared with conventional wound care without HBOT. An HBOT regimen for DFUs usually consists of 30–60 daily sessions of oxygen under pressure in a dedicated hyperbaric chamber (200–250 kPa). This regimen is in sharp contrast to conventional wound care, which usually involves much fewer visits to treating physicians. Patient compliance, ability to pay, or reimbursement coverage creates a significant bias in observational studies. Therefore, placebo and large participation effects associated with HBOT make providing an identical wound care environment for both HBOT and control groups in open-label randomized or observational trials impossible (10). The question remains whether the reported benefits of HBOT in patients with DFUs can be attributed specifically to HBOT.

Two double-blind placebo controlled trials have been reported (11,12). One study included 16 patients (8 patients per arm), and the other analyzed data from 94 patients (49 in HBOT and 45 in sham) (12). Both studies reported beneficial effects on healing but no reduction in amputation rates. A large retrospective study in >700 patients receiving HBOT that used propensity score methods found no benefit of HBOT and possibly an increased risk of amputation in patients treated with HBOT (13). However, many factors affect the actual indications for amputation. These factors include physician practice patterns; the extent of tissue loss; presence or absence of local and systemic infection; patient preferences; cultural, socioeconomic, and insurance status; ability to obtain support and prosthetic devices; and timely access to surgical care (14,15). Therefore, efficacy of HBOT for amputation-sparing effects remains largely unsubstantiated.

We report the results of a double-blind, placebo-controlled clinical trial of HBOT in patients with chronic DFUs receiving comprehensive wound care in a single community-based clinic. The primary goal of the trial was to assess the efficacy of HBOT in reducing indications for amputation (rather than amputation events themselves) in patients with diabetes and chronic ulcers of the lower limb who also receive comprehensive wound care as outlined in Lipsky et al. (16). We also determined whether HBOT significantly improves selected indicators of wound healing.

RESEARCH DESIGN AND METHODS

Trial Design
The general design of this trial is described elsewhere (17). Briefly, the study was a single-center, double-blind, placebo-controlled randomized clinical trial. Patients with diabetes and chronic wounds of the lower limb were randomly assigned to receive either HBOT or sham HBOT in addition to comprehensive wound care. Two parallel research ethics board approvals for the protocol were obtained at both the sponsor’s (data handling and analysis group) and the site investigators’ institutions. The trial was registered before participant enrollment.

Participants
Inclusion criteria were patients ≥18 years of age with type 1 or 2 diabetes referred to a community-based specialized wound care and hyperbaric treatment clinic for the treatment of a lower-limb wound (Wagner grade 2, 3, or 4) (18) persisting for a minimum of 4 weeks. All patients received prior wound care.

Exclusion criteria were any conditions precluding safe treatment in a hyperbaric chamber (see full list in O’Reilly et al. [17]); impending urgent amputation due to ongoing or exacerbated infection; exposed calcaneus bone with no prospect of weight-bearing potential even if the defect has been healed; and patients with major large-vessel, peripheral arterial disease who were possible candidates for revascularization by open surgery or endovascular procedure (as assessed by the vascular surgeon) or those who had undergone such a procedure within the past 3 months.

Sample Size
Sample size was estimated on the basis of a review of the medical literature of previously published randomized controlled trial evidence on the event rates of the primary outcome (i.e., major amputation) in HBOT and standard care groups. Accordingly, a sample size of 47 patients for each group (94 in total) was calculated to provide 90% power for detecting a difference of 28% in the incidence of major amputation (i.e., 39.29% in the placebo group and 11.54% in the HBOT group) between the two groups by a two-sided test for equality (17). Anticipating a 20% dropout rate, the sample size was increased to 118 participants, or 59 in each study arm [i.e., 94 / (1 − 0.20) = 118].

Randomization and Allocation
Concealment
A computerized block randomization schedule with a multiple block size of four was used. All clinical and research personnel as well as patients were blinded to treatment allocation. Only the technician controlling the hyperbaric oxygen chamber was aware of group allocation for each patient, which was maintained in sequential unique opaque envelopes opened as participants were randomly assigned. The concealment was extended through the completion of the data analysis. The groups were only identified as group 1 or group 2 until the analysis of primary and secondary outcomes on an intention-to-treat (ITT) basis was completed.

Interventions

Hyperbaric Oxygen Therapy
Study participants entered the hyperbaric chamber 5 days per week for 6 weeks (30 sessions). HBOT consisted of breathing oxygen for 90 min at 244 kPa of pressure, with 5-min intervals of breathing air for every 30 min of oxygen. Sham sessions consisted of breathing air at ~125 kPa of pressure (equivalent to breathing 27% O₂ by face mask) on the same schedule. This minimum pressure was required to create a sensation of being pressurized and depressurized...
identical to the active treatment group to keep the patients blinded to the allocation. Monoplace chambers (Pan-America Hyperbarics Inc., Richardson, TX) were used. Patients were followed for 6 weeks after the end of hyperbaric sessions and returned to the clinic every week for wound assessment and treatment.

**Wound Care and Dressings**
Weekly clinical assessments for 12 weeks included comprehensive wound care. Care was provided by the multidisciplinary team led by the wound care physician at the study site to include infection control, debridement, prescriptions for off-loading devices, and advanced wound care dressings.

**Data Collection**
Data to evaluate wound healing were collected at screening, at baseline, and weekly throughout the treatment and follow-up phases. At the end of the study period, the participating blinded vascular surgeon determined whether amputation (major or minor) was indicated. Participant clinical data together with digital photographs of the study wound progress were presented to the vascular surgeon. The surgeon had full discretion on a case-by-case basis about whether the status of the wound could be assessed through the digital photography and clinical information alone (as validated by Wirthlin et al. [19] and Houghton et al. [20]) or whether an ad-hoc assessment was based on the following criteria for or undergoing an amputation, univariable logistic regression was used. The primary outcome was analyzed on an ITT basis for all participants. The last observation carried forward was used for patients who did not have 12-week data.

Secondary outcomes included the progress of wound healing assessed by manually measured ulcer width because this measure is less sensitive to the absolute size of the wound (21), surface area (LAWE), and Bates-Jensen wound assessment score. ANCOVA was used to determine a statistically significant difference between treatment received on changes in manual ulcer width, digital surface area, and LAWE and the Bates-Jensen wound assessment score, controlling for baseline wound size. For manual ulcer width, digital surface area, and LAWE, the mean wound measurements were obtained at 6 and 12 weeks for each group, and the group mean changes from baseline were compared. For any missing values at 6 and 12 weeks, we used the value obtained within 1 week. The number of wounds healed at 12 weeks by treatment group was analyzed by univariable logistic regression. The adverse events were compared by treatment allocation by using the \( \chi^2 \) statistic.

All primary statistical analyses were conducted on an ITT basis in accordance with the 2010 Consolidated Standards of Reporting Trials (CONSORT) statement (25). Missing data were imputed by the last observation carried forward, where appropriate. A post hoc analysis was also performed on participants who received at least 27 of the planned 30 treatments or in whom the wound healed before having 30 treatments and was considered a per-protocol analysis.

**RESULTS**

**Enrollment and Patient Characteristics**
Between September 2009 and May 2012, 157 patients were assessed for...
eligibility, and 107 were randomized (Fig. 1). One participant was improperly randomized, and three withdrew their consent after randomization (one in the sham group and two in the HBOT group) and did not receive the allocated treatment. Six in the sham group and 10 in the HBOT group discontinued study participation. After two treatments of HBOT, sepsis complicated with Guillain-Barré syndrome developed in one participant in the HBOT group, requiring hospitalization, and six HBOT group participants were unable to tolerate the chamber sessions as opposed to one in the sham group. As a result, 103 patients were included in the ITT analysis (54 in the sham group and 49 in the HBOT group). Despite randomization, HBOT group participants had diabetes for a longer period than those in the sham group (19.1 vs. 12.4 years, respectively). There were also more patients with type 1 diabetes in the HBOT group than in the sham group (Table 1). More men were randomly assigned to the sham group than to the HBOT group (70.4% vs. 63.3%, respectively), with an average age of 62 years and 61 years, respectively. HbA1c was similar between the groups. The mean number of days with the index wound was 336 (min, max 28, 3,650) in the sham group and 235 days (28, 1,080) in the HBOT group. The mean index ulcer surface area was 6.1 and 5.1 cm² in the sham and HBOT groups, respectively, with most of the wounds classified as Wagner grade 2 and 3. The baseline Bates-Jensen wound assessment scores were similar in both groups.

**Treatment**

Forty-one (76%) participants in the sham group and 30 (61%) in the HBOT group completed at least 30 treatments. Four (7%) and 10 (20%) participants received <11 treatment sessions in the sham and HBOT groups, respectively. More participants in the HBOT group discontinued treatment early (n = 10 [20%]) than those in the sham group (n = 6 [11%]). Most of the discontinuations in the HBOT group were due to participants being unable to tolerate the chambers (n = 6) compared with only one participant in the sham group (Fig. 1). One patient in the sham group discontinued because of the need for amputation.

**Primary Outcome: Meeting Criteria of Need for Amputation or Undergoing Amputation**

In the ITT analysis, a nonsignificant difference was found for HBOT, with 11 (22.5%) HBOT group participants and 13 (24.1%) sham group participants meeting the criteria for major amputation (odds ratio [OR] 0.91 [95% CI 0.37, 2.28], P = 0.846) at the end of the 12-week study period (Table 2). The percentage of amputations recommended of any type (major or minor) was 51% in the HBOT group and 48% in the sham group (1.12 [0.52, 2.43], P = 0.771). The hypothesized benefit of HBOT was a reduction in indication for amputation of 28%, and the results indicated a difference of <3 percentage points. Beyond the adjudicated indication for amputations, only one actual amputation occurred during the 12-week study period, and this was the removal of a toe in a sham group participant. Ten of the 11 participants who received HBOT treatment and met the criteria for major amputation were recommended to have a below-knee amputation, and all of those assessed to require major amputation in the sham group (n = 13) were recommended to have below-knee amputation. Fourteen (28.6%) and 13 (24.1%) participants were adjudicated to undergo minor amputations in the HBOT and sham groups, respectively (1.26 [0.52, 3.04], P = 0.605).

**Figure 1—CONSORT diagram. Tx, treatment. (A high-quality color representation of this figure is available in the online issue.)**
Forty-eight sham group participants and 39 HBOT group participants who completed at least 27 of the 30 planned treatments or healed without discontinuation or withdrawal had end point data (Table 2). A per-protocol post hoc analysis of these groups revealed similar proportions of participants meeting the criteria for major amputation (20.5% and 22.9% in the HBOT and sham groups, respectively; \(95\%\ CI = 0.87\) (95% CI 0.31, 2.43), \(P = 0.787\)) (Table 2).

Secondary Outcomes

Wound Measurements

No significant difference was found at 12 weeks in the reduction in manual width or digital surface area after controlling for baseline wound size. The reduction in manual width was slightly greater in the sham group, with a mean difference of 0.12 cm (95% CI 0.002 cm/week [95% CI 0.16, 0.34], \(P = 0.491\)). The adjusted 12-week reduction in digital surface area was 1.9 cm\(^2\) in the HBOT group and 1.8 cm\(^2\) in the sham group for an adjusted mean difference of 0.037 cm\(^2\) (95% CI 0.0003 cm/week [95% CI 0.016, 0.016], \(P = 0.970\)) (Table 2).

Wound Assessment

The Bates-Jensen wound assessment score was similar for ulcers at baseline in both groups (mean score 34 of a possible 65). Wounds in the sham group improved by 7.5 points compared with 6.9 points in the HBOT group. These differences were not statistically significant (mean difference 0.6 points [95% CI 2.58, 3.64], \(P = 0.735\)) (Table 3 and Fig. 2).

Wound Classification

At 12 weeks, the percentage of participants whose wounds were healed was 20% and 22% in the HBOT and sham groups, respectively (OR 0.87 (95% CI 0.31, 2.43), \(P = 0.787\)) (Table 2).

Adverse Events

One patient in the HBOT group experienced an episode of congestive heart failure, and there were 10 reports of an inability to equalize middle ear pressure during treatment (3 in sham and 7 in HBOT). Four participants in the HBOT group and one in the sham group experienced a hypoglycemic episode during the study. Other adverse events are summarized in Table 4.

CONCLUSIONS

The amputation-sparing effects of HBOT have been reported in two open-label studies (5,8). The current study did not demonstrate an advantage of HBOT combined with comprehensive wound care.
care compared with wound care alone in reducing indications for amputations in patients with DFUs.

That we did not use actual amputation rates in this placebo-controlled trial may be considered a limitation. However, the rate, timing, and decision to amputate are highly variable (15) and influenced by a number of factors (14,26). As a result, to reduce this variability, we decided to have a blinded experienced vascular surgeon adjudicate the wounds for amputation. This procedure replaced all the variable biases with a consistent bias of a single expert-observer for all participants.

The adjuvant HBOT care provided no incremental benefit in improving measures of wound healing. These results are in contrast to several cohort (7,26–28) and open-label randomized trials (5,6,8,9) where no sham placebo was used. The study by Duzgun et al. (8), one of the largest trials published, often is quoted as the justification for HBOT utility in treating diabetic wounds (29). However, these results should be interpreted with caution because it is difficult to explain (outside the observational bias) a zero healing rate (without surgery) in a random cohort of 50 control group patients with Wagner grade 2–4 DFUs over a >1-year period as opposed to the 66% healed in the HBOT group (8). This finding is not consistent with reported healing rates of nonhyperbaric wound care facilities (13,30).

Two randomized placebo-controlled trials of HBOT for the treatment of DFUs have been published (11,12). Abidia et al. (11) reported on eight patients per group and showed a significant difference in the reduction of wound size at 6 weeks in favor of the HBOT group. In the larger trial by Lönndahl et al. (12), the authors chose complete healing of the ulcer as the primary outcome without a predetermined time point at 3-month intervals up to 1 year. Although a clear trend favoring healing in the HBOT group was observed, statistical significance was reached at 9 and 12 months. Both trials reported surprisingly low healing rates in the placebo arms. Lönndahl et al. reported only 3% at 3 months (as estimated from the published figure), and Abidia et al. reported a complete lack of healing within the placebo group (Wagner grade 1 and 2 ulcers only, 0 of 8) at 1 year.

These poor healing rates in the placebo arms are not consistent with the available literature (3,13) and may account for an apparent benefit of HBOT. Both studies (11,12) used sham treatment, which is not benign and possibly interferes with the healing rate of the wounds in the control arm, therefore favoring the HBOT group. The placebo treatment in both studies comprised 30–40 repetitive hyperbaric air exposures to 250 kPa (~50 ft water depth equivalent) for 90 min each. Safety of not only 1 but also 40 cumulative hyperbaric air exposures in elderly patients with diabetes and peripheral arterial disease has never been experimentally evaluated or modeled. This type of placebo can only be considered as extreme

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Data are mean (SE) unless otherwise indicated. HBOT is reference. aOR (95% CI). bMean (SD).

Figure 2—Graphical representation of changes in wound status. A: Wound edge advancement. B: Width reduction. C: Digital surface area. D: Bates-Jensen wound assessment score. Data are mean (95% CI). H, HBOT group; S, sham group.
with regard to decompression stress. Its effects on vascular function in this vulnerable patient population are the least unknown. Clear evidence indicates that single, shorter exposures of healthy young divers to compressed air at slightly higher pressures are associated with evidence of significant gas emboli in venous circulation, proinflammatory changes in peripheral blood, and increases of indirect markers of endothelial injury (31–33). Therefore, the only two previously published randomized placebo-controlled trials do not satisfy criteria for an inert placebo, and their results should not be used in evaluating the efficacy of HBOT for treatment of DFUs.

The major benefit of the current study is that the sham treatment group air pressure exposure was limited to 125 kPa absolute pressure so that ongoing decompression stress and its possible negative effects on wound healing could be avoided in the sham group. Another possible limitation of the study is the relatively short follow-up time of 12 weeks. Efficacy within a similar time frame has been demonstrated in several comparably sized trials of other treatment modalities for DFUs (34–36). Kessler et al. (9) reported that the greatest rate of wound surface area reduction happened within the first 2 weeks of HBOT therapy. Reduction in the wound size within the first 4 weeks of treatment is an excellent predictor of overall healing (23). Had HBOT had a significant influence on accelerating the healing process, we should have been able to observe differences between the groups within the first 3 months of treatment and during the follow-up phase.

The present patient population included individuals with peripheral arterial disease who had either undergone previous vascular intervention or were not candidates for such therapy, similar to the Londahl et al. study (12). It reflects the actual pattern of patient referrals for HBOT. Moreover, 50% of patients with DFUs have a significant neuroischemic component to their ulcers (37).

The current results agree with a large multicenter retrospective cohort study by Margolis et al. (13). The authors used a propensity score matching method to reduce the bias associated with retrospective data (793 patients treated with HBOT vs. 5,466 patients treated with standard therapies). The study failed to find a beneficial treatment effect of HBOT regardless of wound size and actually found higher rates of amputation in the HBOT cohort.

The current study did not find a significant benefit associated with adjuvant HBOT. A subset of diabetic lower-extremity wounds may benefit from HBOT; however, until such a subset can be confirmed to exist in future studies, we cannot recommend the use of adjuvant HBOT for reducing indications for amputation or for facilitating healing in this patient population.

**Funding.** This study was funded by an unconditional research grant from the Ontario Ministry of Health and Long-Term Care (06129).

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** L.F. and D.J.O. contributed to the study design, data research and collection, and writing, review, and editing of the manuscript. J.M.B. and W.J. contributed to the study design, data research and collection, and review and editing of the manuscript. G.O. contributed to the data research and collection and review and editing of the manuscript. R.G. contributed to the study design and review and editing of the manuscript. R.B.H. contributed to the data verification, statistical analysis, and review and editing of the manuscript. L.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** Parts of this study were presented during a pro and con debate lecture by L.F. at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015, and during a lecture by L.F. at the Diabetic Foot Global Conference (DFCON 2013), Los Angeles, CA, 21–23 March 2013.

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