Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study

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Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. Undersea Hyper Med 1997; 24(3):175-179.—The purpose of this study was to prospectively evaluate the effect of hyperbaric oxygen (HBO₂) on the healing of diabetic lower extremity wounds. Ten consecutive insulin-dependent diabetic patients with chronic lower extremity wounds were referred for HBO₂ treatment. The control group consisted of five patients, two claustrophobic and three rural. The latter refused HBO₂ treatments because of logistic reasons. Five patients underwent 30 HBO₂ treatments in the problem wound protocol (100% oxygen, 2 atm abs, 2 h/day, 5 days/wk). All patients were evaluated with transtibial wound oxygen measurements and had an initial surgical debriding of the wound. Weekly tracings of the wound surface area were made by a nurse or resident who was blinded to the group assignment. At the end of 7 wk, the mean wound area expressed as a percentage of pretreatment baseline area was compared between groups (analysis of variance, Duncan’s post hoc). No significant differences were noted between groups with respect to age, gender, baseline wound area, wound site O₂ tension, or presence of osteomyelitis. At the completion of each of the 7-wk treatment periods, a significantly greater reduction in wound surface area was noted in the HBO₂ vs. the control group (P < 0.05). HBO₂ treatment significantly reduced wound size compared to controls in this small, non-randomized prospective study. These results should serve as a basis for larger multicenter prospective, randomized, double-blind controlled studies to definitively evaluate the effect of HBO₂ on the healing of diabetic foot wounds.

hyperbaric oxygenation, diabetic foot, prospective study

Foot lesions in patients with diabetes mellitus are a major health problem with significant morbidity and mortality and are associated with high economic and social costs. It has been estimated that 20–25% of all hospital admissions of patients with diabetes are due to foot lesions (1), and that foot complications are responsible for more inpatient hospital days than all other diabetic complications combined (1). About 2.5% of persons with diabetes will develop a foot ulcer each year (2). Some of these lesions will deteriorate to gangrene or severe deep infection, necessitating minor or major amputation. Diabetes is the leading cause of lower extremity amputations in the United States, accounting for 50–70% of all non-traumatic lower extremity amputations (3–5). The rate of lower extremity amputations among persons with diabetes is 15–40 times greater than the rate in persons without diabetes (3,4). Ulceration of the foot is the major precursor lesion leading to amputation in persons with diabetes (6,7).

The adjunctive use of hyperbaric oxygen (HBO₂), in combination with surgical debridement, local wound care, appropriate antibiotic therapy, and control of blood glucose, has added an important modality in the management of chronic non-healing diabetic wounds. The pathophysiology of diabetes and its sequelae leads to ischemia and hypoxia at the cellular level in the diabetic foot. HBO₂ therapy can elevate tissue oxygen levels and thus promote wound healing due to the secondary effects of hyper-oxygenation, which include bacteriostasis of anaerobic organisms, enhancement of neutrophil oxidative killing of bacteria, and promotion of fibroblast proliferation, collagen production, and neovascularization in the healing wound (8,9).

Diabetic foot ulcers comprise the largest group of non-healing problem wounds and are the most common wounds referred for HBO₂ treatment. However, there have been few controlled prospective studies evaluating the efficacy of HBO₂ in healing such wounds. Thus, the purpose of this study was to prospectively evaluate the effect of HBO₂ on chronic non-healing wounds in patients with insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS

Study groups: Ten consecutive, long-standing (>10 yr) insulin-dependent diabetic patients with chronic non-
healing lower extremity wounds were referred for HBO$_2$ treatment. One wound was present on the ankle and the remaining involved the foot. Two claustrophobic and three rural patients refused treatment and thus served as the control group. The remaining five patients comprised the treatment group and underwent HBO$_2$ therapy using a protocol within the guidelines of the UHMS HBO Committee Report (10). All patients were maintained on their insulin treatment regimens as prescribed and managed by their personal physician and/or endocrinologist.

Data collection: Basic demographic data were collected on all patients. Baseline wound transcutaneous oxygen tension (TePO$_2$) (TCM3/TINA, Radiometer America Inc, Westlake, OH) was measured in a standardized fashion in noninflamed skin 1 cm medially away from the wound edge at the midpoint of the ulcer, with measurements being recorded at room air, 100% O$_2$ by face mask, and (treatment group only) HBO$_2$ at 2.0 atm abs. Measurements in the second intercostal space at room air were used as a standard reference.

After informed consent, all patients underwent initial surgical debridement of the wound, usually in the operating room. Sharp scalpel debridement of the peripheral skin edge and all nonviable tissue was done on all patients. If osteomyelitis was present, rongeur debridement to bleeding clinically noninfected bone was done. Standard postoperative wound management consisted of 1% Silvadene (silver sulfadiazine) non-occlusive dressing changes twice a day for 5 days followed by saline-moistened sterile gauze dressing changes twice a day, either by a home nurse or hyperbaric technician, for the entire treatment period. Patients with cellulitis, deep soft tissue infection, or osteomyelitis were treated with culture-specific intravenous antibiotics based on deep cultures taken from the wound at the time of debridement. In addition, the intervention cohort underwent HBO$_2$ treatments (Sechrist Industries Inc, Anaheim, CA, model 2500 monoplace chamber) consisting of 100% O$_2$ for 120 min per session at a depth of 2.0 atm abs. Patients were treated 5 days/wk for a total of 30 treatments. All patients were seen weekly in the office for wound assessment.

Baseline wound surface area (WSA) was measured after initial surgical debridement. Weekly tracings of WSA onto nongridded transparent film were made by a nurse or resident who was blinded to the group assignment. Tracings were digitally entered onto a computer and the WSA analyzed and measured using computerized planimetry (SigmaScan/Image 1.2, Jandel Scientific Software, San Rafael, CA). Wound surface area was expressed in square centimeters and as a percentage of the initial baseline pretreatment WSA. Endpoints were designated as complete healing of a wound or amputation of the affected extremity.

Statistical methods: Results are reported in text and figures as mean ± standard error of the mean (SEM). Age and baseline WSA were compared by Student’s t test for statistical differences. Mean WSA as a percentage of the initial baseline pretreatment WSA was compared between the two groups using analysis of variance (ANOVA) and Duncan’s post hoc analysis. Upon reaching the endpoints of complete healing or amputation, the final measurement was entered once and then removed for calculation of subsequent mean WSAs. Significance for all statistical analysis was accepted for $P < 0.05$.

RESULTS
All patients had insulin-dependent diabetes mellitus. No significant differences were noted between groups with respect to age, gender, baseline wound area, reference and wound site TePO$_2$, or the presence of osteomyelitis (Table 1). The duration of the wounds varied but, in general, had been present for greater than 6 mo. All patients had undergone prior evaluation by a vascular surgeon. Two patients in the control group had undergone lower extremity arterial bypass; all other patients were without significant macrovascular disease amenable to surgical intervention.

Based on weekly measurements of mean WSA expressed as a percentage of the pretreatment baseline, a significantly greater reduction in WSA was seen in the HBO$_2$ treatment group compared with controls at each of the 7 wk of the study (Fig. 1). For the duration of the study as a whole, ANOVA demonstrated that the reduction in WSA was significantly greater in the HBO$_2$ treatment group vs. controls ($P < 0.05$).

After completion of the 7-week study, all patients were followed for 4–6 mo. In the control group, four of five (80%) patients had persistent non-healing of their wounds.

| Table 1: Baseline Patient Characteristics (mean ± SEM) |
|---------------------|-------------|-------------|
| Characteristics     | Control, n = 5 | HBO$_2$ Therapy, n = 5 |
| Age, yr             | 53.8±3.50   | 63.6±3.96   |
| Gender male:female  | 4:1         | 4:1         |
| Baseline wound surface Area, cm$^2$ | 4.4±1.50   | 6.02±1.73   |
| Reference, room air TePO$_2$, mmHg | 60.0±2.12 | 53.4±4.35 |
| Wound TePO$_2$, mmHg at Room air | 35.3±2.30 | 12.0±2.91  |
| Mask, 100% O$_2$    | 80.0±16.34  | 71.2±25.23  |
| HBO$_2$ at 2.0 atm abs | N.A.       | 562.4±55.79 |
| Osteomyelitis       | 60%, 3/5    | 80%, 4/5    |
HYPERBARIC OXYGEN FOR DIABETIC WOUNDS

![Graph showing Wound Surface Area (%) Change over time for NO TREATMENT and HBO TREATMENT](image)

FIG. 1—Weekly mean WSA as a percentage of the initial baseline pretreatment WSA for control (open bars) and HBO (solid bars) treatment groups. Asterisk = $P < 0.05$ vs. controls.

at the end of follow up; the remaining patient developed a stable callus over the wound. None required amputation. In the HBO treatment group, four of five (80%) patients had spontaneous healing of their wounds; the remaining patient underwent surgical coverage with a lateral calcaneal flap. There were no amputations. At the end of the study, $\chi^2$ analysis of differences among proportions shows a $P = 0.0578$ comparing healed wounds between groups.

DISCUSSION

Many factors come into play in the chronic, non-healing wound, particularly in the patient with diabetes. Edema, infection, anemia, ischemia, and poor perfusion are all impediments to the normal processes of wound healing. The consequence of most of these factors is low O$_2$ tension and a state of cellular hypoxia, which adversely affect neutrophil, macrophage, and fibroblast function during inflammation and repair. In studies of significant independent predictors of foot ulceration, the strongest risk factor was impaired cutaneous oxygenation (11–14). In general, TcPO$_2$ values below 30 mmHg indicate that the wound probably will not heal without adjunctive treatment.

Hypoxia as a result of ischemia and poor perfusion must be addressed in any chronic non-healing wound. Vascular insufficiency in patients with diabetes from peripheral arterial disease appears earlier, tends to be more diffuse and more distal in the arterial system, particularly below the knee and trifurcation in the tibial and peroneal arteries (15). Vascular evaluation is the first priority to correct treatable vascular lesions. If the patient has non-reconstructible anatomy or does not respond satisfactorily despite revascularization, then HBO therapy may be indicated to improve tissue oxygenation. Although toe pressures frequently correlate with TcPO$_2$ readings, it is not unusual to see a toe pressure that is normal (or falsely elevated due to calcified vessels) and a low TcPO$_2$, particu-
hospitalized patients with grade 3 and 4 diabetic foot wounds, Oriani et al. (28) demonstrated that the healing rate significantly increased from 66 to 95% with concurrent reduction in the amputation rate from 33 to 5% by the addition of HBO2 to conventional treatment. In a prospective, non-randomized controlled study, Baroni et al. (29) evaluated the efficacy of HBO2 in hospitalized patients with diabetic foot wounds. In the control group of 10 patients who refused HBO2 treatment, only 1 went on to complete healing, 5 showed no change, and 4 required amputation. In the HBO2 group of 18 patients, 16 progressed to complete healing with only 2 requiring amputation. In addition, they reported retrospectively that 17 of 42 patients (42%) at their center with diabetic foot wounds required amputation in the 3 yr before the use of HBO2, compared with 8 of 71 (11%) over 3 yr after the addition of HBO2 to treatment regimens (29). In a prospective, randomized study of 30 patients evaluating the addition of HBO2 to conventional therapy in the management of chronic diabetic foot lesions, only 2 patients in the HBO2 group required amputation compared to 7 in the control group (30). Faglia et al. (31) evaluated the effectiveness of systemic HBO2 therapy on decreasing major amputation rate in a prospective, randomized study of hospitalized diabetic patients. Of 68 subjects who completed the protocol, 33.3% of the non-treated group and only 8.6% of the HBO2-treated group underwent major amputation (P = 0.016) (31).

Our own results demonstrated that the use of adjunctive HBO2 significantly reduced wound size compared with controls in patients with IDDM. This effect was evident after the first week of HBO2 treatment and persisted through all subsequent weeks of the study. Insight on the physiologic explanations for these results may be provided by extensive research by Hunt (32) on the effect of O2 in wound healing. Angiogenesis, which requires the deposition of an adequate supporting collagen matrix which in turn provides the nutrients necessary for further collagen synthesis in a delicately balanced relationship, is accelerated by hypoxia. The O2 gradient between normal tissue next to the wound and the wound itself drives the repair process (33). When this gradient is exaggerated by various modalities such as HBO2, healing is more able to proceed at a normal pace. This leads to faster and more effective healing as seen in our HBO2 population in which the periwound TcPO2 was raised from a mean of 12 mmHg in room air to more than 560 mmHg in the hyperbaric chamber. In contrast, the control wounds had O2 tensions (mean 35 mmHg) which were marginal at best for effective wound healing. In other words, HBO2 probably established an early baseline wound microenvironment more optimal for the promotion of wound healing, which resulted in the more rapid decrease in wound area seen in the first week and throughout the study in the HBO2 group compared with controls. In addition, a continuing effect on wound healing persisted after HBO2 therapy was completed in week 6: 80% of wounds treated with HBO2 progressed to complete healing spontaneously vs. 20% in the control group. Although the rate of decrease in wound size seemed to be similar between the two groups after the initial disparity in the first week, it seems likely that the rate of decrease in the control group would have leveled off after 7 wk because these patients had persistence of their ulcers upon long-term follow up, whereas the majority of the HBO2 group went on to spontaneous healing.

It must be emphasized that HBO2 is an adjunctive therapy to the many other components essential to the management of chronic non-healing foot wounds, particularly in patients with diabetes. These include adequate surgical debridement, appropriate antibiotic therapy, local wound care, metabolic control, non-weight bearing or pressure-relief showeware and orthosis, and correction of vascular insufficiency if possible (13). In this study, HBO2 used in conjunction with these modalities produced favorable results.

Despite the small numbers of patients in this prospective, non-randomized study, HBO2 was demonstrated to be efficacious in the healing of chronic diabetic foot wounds. The results of this and other studies should provide the impetus and basis for larger multicenter prospective, randomized, double-blinded controlled studies to definitively evaluate the effect of HBO2 therapy on the healing of diabetic foot wounds.

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