Effect of Hyperbaric Oxygen Therapy on Healing of Diabetic Foot Ulcers

Arife Polat Duzgun, MD,[1] Hakan Ziya Satır, MD,[2] Omer Ozozan, MD,[1] Barıs Saylam, MD,[1] Bahadır Kulah, MD, MS, FACS,[3] and Faruk Coskun, MD[4]

Hyperbaric oxygen therapy can be used as an adjunct to standard wound care in the treatment of diabetic patients with foot ulcers. We undertook a prospective, randomized investigation of the use of hyperbaric oxygen therapy versus standard therapy for the treatment of foot ulcers in diabetic patients. A number of demographic variables were analyzed in regard to wound healing. We noted that foot ulcers in patients in the hyperbaric oxygen therapy group were more likely to heal, and were more likely to undergo amputation distal to the metatarsophalangeal joint compared with those patients receiving standard therapy without hyperbaric oxygen. We feel that hyperbaric oxygen therapy should be considered a useful adjunct in the management of foot ulcers in diabetic patients. Level of Clinical Evidence: 2 (The Journal of Foot & Ankle Surgery 47(6):515–519, 2008)

Key Words: amputation, diabetic foot ulcer, hyperbaric oxygen therapy, wound healing

Currently, standard therapy (ST) for lower extremity wounds in diabetic patients entails wound debridement, off-loading, systemic antibiotic therapy, and supportive medical therapy in an effort to heal wounds within a reasonable period of time, generally considered to be up to 4 to 5 months. Another current option for the treatment of diabetic patients with lower extremity ulceration is hyperbaric oxygen therapy (HBOT). HBOT is a systemic treatment option, wherein the patient breathes 100% oxygen for a specified period of time in a pressurized chamber. In the 1970s, the clinical use of HBOT in patients with diabetic foot wounds was initiated by the positive treatment results reported in a number of case reports and series (1–12). Faglia et al (5) prospectively reported on 70 diabetic patients who received HBOT, and observed a decreased rate of major amputations (transtibial or more proximal) in comparison with standard therapy. Similarly, several other studies also demonstrated that HBOT decreased the risk of major amputation in diabetic patients with foot ulceration (1, 5–7, 12). In a review of 6 studies, HBOT was observed to decrease the risk of major lower extremity amputations in 118 patients (7). In yet another investigation, involving 55 patients with diabetic foot ulcers that extended deep to the deep fascia, it was noted that the use of HBOT decreased the prevalence of major amputation (8).

HBOT has been shown to promote healing in diabetic wounds by means of its anti-edema, antibacterial, and neovascularization effects (13–18). Because of its apparently beneficial effect on wound healing, there is a trend toward resorting to the use of HBOT in cases of problematic wounds such as diabetic foot ulcers, particularly when there is a concern for neovascularization (1–9, 19). The primary aim of this prospective randomized controlled trial was to evaluate the effects of HBOT on diabetic foot ulcers, and to compare this form of therapy to standard wound care (standard therapy, ST).

Patients and Methods

After receiving approval from the Ethical Committee of Ankara Numune Teaching and Research Hospital, Turkey, consecutive patients who were admitted to the Emergency Surgical Department between January 2002 and December 2003 for the treatment of infected diabetic foot ulceration were evaluated for potential inclusion in the investigation. In addition to receiving standard medical assessment, each patient was evaluated to determine whether HBOT was contraindicated (Table 1) (20). Diabetic patients were considered eligible if they were at least 18 years of age, and if they had a foot wound that had been present for at least 4 weeks despite appropriate local and systemic wound care.

Address correspondence to: Faruk Coskun, MD, Sehit Adem Yavuz Sokak No: 7/11, 06100-Kizilay, Ankara, Turkey. E-mail: farukcoskun@mynet.com.

[1]General Surgeon, Ankara Numune Teaching and Research Hospital, Department of 3rd Surgery, Ankara, Turkey.

[2]General Surgeon, Ankara Numune Teaching and Research Hospital, Family Practice, Ankara, Turkey.

[3]Associate Professor of Surgery, Ankara Numune Teaching and Research Hospital, Department of 3rd Surgery, Ankara, Turkey.

[4]Associate Professor of Surgery, Director of 3rd Surgery Department, Ankara Numune Teaching and Research Hospital, Department of 3rd Surgery, Ankara, Turkey.

Financial Disclosure: None reported.

Conflict of Interest: None reported.

1067-2516/08/4706-0005$34.00/0

doi:10.1053/j.jfas.2008.08.002

TABLE 1 Contraindications to hyperbaric oxygen therapy*

Untreated pneumothorax
Obstructive pulmonary disease
History of otic surgery
Upper respiratory tract infection
Febrile state (since fever decreases seizure threshold)
History of idiopathic convulsion
Hypoglycemia
Current corticosteroid, amphetamine, catecholamine, or thyroid hormone use

*Adapted from Jain (20).

TABLE 2 The Wagner* classification of diabetic foot ulceration

Grade	Clinical description
0	No open ulcer, high risk
1	Superficial ulcer with subcutaneous involvement
2	Deep ulcer with tendon or joint involvement
3	Deep ulcer with bone involvement
4	Wet or dry gangrene (forefoot), without cellulitis
5	Generalized (whole foot) gangrene

*Adapted from Wagner (21).

The foot wounds were categorized according to a modification of the Wagner classification (Table 2) (21), and the diagnosis of osteomyelitis was made based on bone biopsy at the time of surgical intervention. Moreover, photographic images were obtained before and after the therapy. All of the patients were further evaluated in an effort to determine whether or not they would be suitable candidates to undergo HBOT. After confirming eligibility, the patients were randomly assigned to the standard treatment group or the standard therapy plus HBOT group, using a random number table and allocating patients to the treatment groups according to a predetermined sequence wherein consecutively enrolled patients corresponding to an even random number received ST, and those corresponding to an odd random number received ST + HBOT. We continued this process until we had 50 participants in each treatment group.

ST entailed daily wound care, including dressing changes and local debridement at bedside or in the operating room, as well as amputation when indicated. Infection controls were carried out by clinical follow-up, and by performing culture-antibiograms of surgically obtained specimens to determine appropriate antibiotic therapy. In the HBOT group, standard therapy was supplemented by hyperbaric oxygen treatments administered at a maximum working pressure of 20 atmospheres absolute (ATA), using a unichamber pressure room (Patterson Companies, Inc., St. Paul, MN) employing a volume of 10 m^3 at 2 to 3 ATA for 90 minutes. Treatment was administered as 2 sessions per day, followed by 1 session on the following day, alternating throughout the course of therapy, which typically extended for a period of 20 to 30 days.

A number of independent variables were measured and recorded, including age, gender, duration of diabetes, hypertension, lipid-lipoprotein levels (triglyceride, cholesterol, high-density lipoprotein, low-density lipoprotein, and very low density lipoprotein), obesity, smoking habits, and glycosylated hemoglobin (HbA1c). Patients with a body mass index (BMI) of 30 or greater were defined as obese. Smokers were defined as either current (active smokers or those who had quit within 2 months of presentation), or nonsmokers. High lipid-lipoprotein levels were defined as follows: triglyceride 180 mg/dL or higher, cholesterol 200 mg/dl or higher, and low-density lipoprotein 160 mg/dL or higher. Outcome variables were defined as (1) total closure of the wound without the need for surgical intervention in the operating room (complete cure with bedside debridement); (2) graft or flap closure required; (3) amputation distal to the metatarsophalangeal joints (MTPJ) (distal amputation) required to achieve closure; (4) amputation proximal to the metatarsophalangeal joints (proximal amputation) required to achieve closure; (5) no change (defined as no sign of healing during the course of treatment); and (6) operative surgical debridement (in the operating room) of the wound was all that was required to achieve closure.

Statistical analyses were performed using a personal computer running SPSS 11.0 (SPSS, Inc. Chicago, IL) for Windows 98 (Microsoft, Inc., Redmond, WA). Two-tailed unpaired Student *t* tests were used to analyze continuous numeric data, including age, duration of diabetes, and HbA1c measurements, whereas the Mann Whitney *U* (Wilcoxon rank sum) test was used to analyze categorical data, including gender, hypertension, obesity, lipid-lipoprotein levels, smoking status, insulin dependence, and ulcer grade. Statistical significance was defined at the 5% ($P \leq .05$) level.

Results

A total of 100 patients were determined to be eligible for participation in the investigation and, in accordance with the random allocation protocol, 50 of these were allocated ST and the other 50 to ST combined with HBOT. The overall mean duration of follow-up was 92 ± 12 weeks. The baseline characteristics of the treatment groups are depicted in Table 3. In the ST group there were 50 patients, and the female-to-male ratio was 23:27, their mean age was 63.00 ± 9.15 years, and their mean duration of diabetes was 15.88 ± 5.56 years. In the HBOT group, there were 50 patients, and the female-to-male ratio was 13:37, their mean age was 58.1 ± 11.03 years, and their mean duration of diabetes was 16.90 ± 6.24 years. There were no statistically significant differences between the groups in regard to age, duration of diabetes, the type and treatment of their diabetes, hypertension, lipid-lipoprotein levels, and ulcer grade.

TABLE 3 Baseline characteristics of the cohort by treatment groups (N = 100)*

Independent variable	ST (n = 50)	HBOT (n = 50)	*P* value†
Male gender	27 (54)	37 (74)	<.05
Age, y	63.3 ± 9.15	58.1 ± 11.03	>.05
Duration of diabetes, y	15.88 ± 5.56	16.9 ± 6.24	>.05
Hypertension, yes/no	28 (56)	32 (64)	>.05
Obesity, body mass index > 30	23 (46)	40 (80)	<.05
Current cigarette smoker‡	20 (40)	36 (72)	<.05
High lipid-lipoprotein level§	27 (54)	31 (62)	>.05
Glycosylated hemoglobin (mg/dL)	8.7 ± 2.9	8.0 ± 1.9	>.05
Insulin dependent (yes/no)	45 (90)	41 (82)	>.05
Ulcer grade‖			
2	12 (24)	6 (12)	>.05
3	18 (36)	19 (38)	>.05
4	20 (40)	25 (50)	>.05

Abbreviations: ST, standard therapy; HBOT, hyperbaric oxygen therapy.
*Results presented as either mean ± SD for continuous numeric data, or count and percent for categorical data.
†Probability of the null hypothesis calculated using 2-tailed, unpaired Student *t* test for continuous numeric data and the Mann Whitney *U* (Wilcoxon rank sum) test for categorical data.
‡Current smokers = active smokers or those who had quit within 2 months of presentation.
§High lipid-lipoprotein levels = triglyceride ≥ 180 mg/dL, cholesterol ≥ 200 mg/dL, and low-density lipoprotein ≥ 160 mg/dL.
‖Adapted from Wagner (21), Table 2.

Statistically significant differences were identified between the proportion of males, obese patients, and smokers, all of which were more prevalent in the HBOT group (Table 3). When we compared the result of ST to ST + HBOT, a number of statistically significant findings were made (Table 4). Specifically, there were zero (0%) patients in the ST group who healed without surgery performed in the operating room, versus 33 (66%) of the patients in the group receiving HBOT healed without going to the operating room. To achieve wound coverage and healing, 50 (100%) of those in the ST group required either operative debridement in the operating room, an amputation, or the use of a flap or skin graft; whereas 8 (16%) of those in the group receiving HBOT required these forms of surgical management. In regard to distal (distal to the MTPJ level) versus proximal (proximal to the MTPJ level) amputation, 24 (48%) of those in the ST group underwent distal amputation whereas 17 (34%) of them required proximal amputation. In the group receiving HBOT, 4 (8%) underwent distal amputation, and zero (0%) required proximal amputation. In regard to observing no change in wound healing, zero (0%) patients in the ST group and 9 (18%) in the group receiving HBOT displayed this outcome over the course of the observation period. Although all of these findings were statistically significant when nonparametric null hypothesis tests were calculated, the association with the risk factor variables changed considerably (>10%) when univariate and multiple variable logistic regression equations were computed for ulcer grade and HBOT, indicating confounding between these variables (results not shown).

Discussion

It is generally understood that tissue hypoxia can be a significant factor in the etiology of nonhealing foot ulcers in diabetic patients. Through its correction of peripheral ischemia, HBOT may be useful in promoting healing when other modalities fail (17, 20, 22). To this end, HBOT promotes healing in a variety of ways. First, the oxygen gradient that is produced by HBOT promotes the formation of new vessels required for wound healing, and increases fibroblast proliferation and collagen production (15, 17–19). In addition, HBOT has bactericidal and bacteriostatic effects on both aerobic and anaerobic bacteria through the action of the super oxide enzyme, which acts more rapidly at high oxygen tensions (≥30 to 40 mm Hg) (20). HBOT has also been shown to have synergistic effects with aminoglycosides, trimethoprim, nitrofurantoin, and sulfisoxazole (23). Furthermore, hyperoxic vasoconstriction that takes place during HBOT reduces capillary pressure and increases vascular permeability. The resulting decrease in transcapillary fluid transfer increases extravascular fluid resorption, which reduces lower extremity edema (20, 24).

In animal studies, Niinikoski has demonstrated that wound healing was an oxygen dependent process by measuring transcutaneous oxygen pressure $TcP0_2$ (13, 14). By employing the same technique, Sheffield (17) demonstrated that chronic tissue hypoxia could be corrected by HBOT. Guidelines based on transcutaneous oximetry and ulcer grade classification can be used to aid the clinician in determining which patients are suitable candidates for HBOT (14, 15, 22, 23). In clinical investigations, some clinicians used transcutaneous oximetry only for follow-up, after initially basing their decision on wound grade and other factors. The Wagner classification (21) is commonly used to grade severity of diabetic foot ulcers, although the system can be criticized for lacking sensitivity and specificity, and for not taking into consideration differences between neuropathic and vasculopathic diabetic foot ulcers. Wyss et al (25) have demonstrated that wound healing can be hindered in conditions involving decreasing transcutaneous oxygen levels. Despite efforts to provide guidelines regarding the use of HBOT, many clinicians still rely on clinical acumen rather than transcutaneous oxygen measure-

TABLE 4 Outcomes by intervention and ulcer grade (N = 100)*

Outcome†	Ulcer grade 2 (n = 18)			Ulcer grade 3 (n = 37)			Ulcer grade 4 (n = 45)		
	ST (n = 12) count (%)	HBOT (n = 6) count (%)	*P* value‡	ST (n = 18) count (%)	HBOT (n = 19) count (%)	*P* value‡	ST (n = 20) count (%)	HBOT (n = 25) count (%)	*P* value‡
Healed (n = 33)	0	6 (100)	<.05	0	13 (68)	<.05	0	14 (56)	<.05
Graft or flap (n = 4)	0	0	—§	0	0	—	0	4 (16)	<.05
Distal amputation (n = 28)	4 (33)	0	<.05	17 (94)	1(5)	<.05	3 (15)	3 (12)	<.05
Proximal amputation (n = 17)	0	0	—§	0	0	—	17 (85)	0	<.05
Debridement (n = 9)	8 (67)	0	<.05	1 (6)	0	<.05	0	0	—
No change (n = 9)	0	0	—§	0	5 (27)	<.05	0	4 (16)	<.05

Abbreviations: ST, standard therapy; HBOT, hyperbaric oxygen therapy.
*Results presented as count and percentage.
†Outcomes: Healed = complete closure without debridement in the operating room, Graft or flap = graft or flap closure required, Distal amputation = amputation distal to metatarsophalangeal joints, Proximal amputation = amputation proximal to the metatarsophalangeal joints, Debridement = standard therapy wound debridement, Debridement = operative surgical debridement (in the operating room) of the wound was all that was required to achieve closure, No change = failure to heal during the course of treatment.
‡Probability of the null hypothesis calculated using the Mann Whitney *U* (Wilcoxon rank sum) test.
§No matching, n = 0, in this subcategory.

ments to determine when a patient could benefit from the use of HBOT (22).

In our study, ulcers were categorized in accordance with Wagner's classification. Importantly, and likely due to randomization, a statistically significant difference in the baseline severity of the ulcers was not observed between the treatment groups (Table 3). Interestingly, however, there was a higher prevalence of males, obese patients, and smokers in the HBOT group and, despite these traditionally harmful risk factor variables (in regard to wound healing), those in the HBOT group fared more favorably than did those in the ST group (Table 3). This supports the idea that HBOT has a strong beneficial effect on wound healing in diabetic patients since, even in the presence of risk factors that are typically harmful, more patients healed their lower extremity wounds (Table 4).

Despite our use of treatment allocation via randomization, a number of potential limitations may have biased our results. For instance, we did not distinguish between foot ulcers that were primarily attributable to ischemia versus those attributable to both peripheral ischemia and prolonged pressure that went undetected due to neuropathy. Moreover, we did not examine the relationship of complications and the cost of the different therapeutic interventions in regard to the outcomes. We are also not able to explain, beyond chance, the statistically significant differences observed between the treatment groups in regard to the baseline characteristics of the patients.

In conclusion, this study showed that the use of HBOT in the treatment of diabetic foot ulcers statistically significantly improved the prevalence of healing in foot ulcers of diabetic patients. HBOT also diminished the prevalence of amputations, and when amputation was required, none of the amputations were localized proximal to the MTPJs. Moreover, HBOT appears to reduce the need for costly and technically more involved surgical interventions, such as skin flaps and grafts, as well as amputations and debridements that require the operating room. We believe that HBOT is a useful adjunct in the treatment of nonhealing diabetic foot ulcers, and that the cost of HBOT itself will be reduced as it becomes more widely available in the clinical setting, and as further knowledge of its other advantages, such as limited side effects and relative safety, become more widely appreciated.

References

1. Baroni G, Porro T, Faglia E, Pizzi G, Mastropasqua A, Oriani G, Pedesini G, Favales F. Hyperbaric oxygen in diabetic gangrene treatment. Diabetes Care 10:81–86, 1987.
2. Oriani G, Magni R, Michael M, Musini A, Durante A, Campagnoli P, Brancato R. Assessment of visual contrast sensitivity in hyperbaric oxygen. Undersea Hyperb Med 21:387–390, 1994.
3. Oriani G, Faglia E, Favales F. Hyperbaric oxygen (HBO) in the treatment of diabetic gangrene. Proceedings of the XXI Annual Meeting of European Underwater and Baromedical Society, p. 120, 1995, European Underwater and Baromedical Society, Hainault, Ilford, Essex, United Kingdom, June 28-July 1, 1995.
4. Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. Undersea Hyperb Med 24:175–179, 1997.
5. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Barbano P, Puttini M, Palmieri B, Brambilla G, Rampoldi A, Mazzola E, Valenti L, Fattori G, Rega V, Cristalli A, Oriani G, Michael M, Morabito A. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. J Diabetes Complications 12:96–102, 1998.
6. Kalani M, Jörneskog G, Naderi N, Lind F, Brismar K. Hyperbaric

oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. J Diabetes Complications 16:153–8, 2002.
7. Roeckl-Wiedmann I, Bennett M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. Br J Surg 92:24–32, 2005.
8. Albuquerque E, Sousa J. Long-term evaluation of chronic diabetic foot ulcers, non-healed after hyperbaric oxygen therapy [in Portuguese]. Rev Port Cir Cardiothorac Vasc 12:227–236, 2005.
9. Cianci P. Advances in the treatment of the diabetic foot: Is there a role for adjunctive hyperbaric oxygen therapy? Wound Repair Regen 12: 2–10, 2004.
10. Seaman S. The role of the nurse specialist in the care of patients with diabetic foot ulcers. Foot Ankle Int 26:19–26, 2005.
11. Cianci P. Adjunctive hyperbaric oxygen therapy in the treatment of the diabetic foot. J Am Podiatr Med Assoc 84:448–455, 1994.
12. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev (2):CD004123, 2004.
13. Niinikoski J. Hyperbaric oxygen therapy of diabetic foot ulcers, transcutaneous oximetry in clinical decision making. Wound Repair Regen 11:458–461, 2003.
14. Niinikoski JH. Clinical hyperbaric oxygen therapy, wound perfusion, and transcutaneous oximetry. World J Surg 28:307–311, 2004. Epub Feb 17, 2004.
15. Wattel F, Mathieu D. Oxygen and wound healing [in French]. Bull Acad Natl Med 189:853–864, 2005.
16. Heng MC, Harker J, Csathy G, Marshall C, Brazier J, Sumampong S, Paterno Gomez E. Angiogenesis in necrotic ulcers treated with hyperbaric oxygen. Ostomy Wound Manage 46:18–28, 30–2, 2000.
17. Sheffield JP. Tissue oxygen measurements. In *Problem Wounds: The Role of Oxygen*, pp 17–51, edited by JC Davis, TK Hunt, Elsevier, New York, 1988.
18. Cianci PE, Petrone G, Drager S, Lueders H, Lee H, Shapiro R. Salvage of the problem wound and potential amputation with wound care and active hyperbaric oxygen therapy: an economic analysis. J Hyperbaric Med 3:127–141, 1988.
19. Kessler L, Bilbault P, Ortéga F, Grasso C, Passemard R, Stephan D, Pinget M, Schneider F. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care 26:2378–2382, 2003.
20. Jain KK. Physical, physiological and biochemical aspects of hyperbaric oxygenation. In *Textbook of Hyperbaric Medicine*, pp 480–495, edited by Jain KK, Neubauer R, Correa JG, Hogrefe & Huber, Toronto, 1990.
21. Wagner FW. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 2:64–122, 1981.
22. Fife CE, Buyukcakır C, Otto GH, Sheffield PJ, Warriner RA, Love TL, Mader J. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients. Wound Repair Regen 10:198–207, 2002.
23. Brakora MJ, Sheffield PJ. Hyperbaric oxygen therapy for diabetic wounds. Clin Podiatr Med Surg 12:105–117, 1995.
24. Strauss MB. Crush injury and other acute traumatic peripheral ischemias. In *Hyperbaric Medicine Practice*, pp 525–550, edited by EP Kindwall, Best Publishing Company, Flagstaff, 1995.
25. Wyss CR, Harrington RM, Burgess EM, Matsen FA. Transcutaneous oxygen tension as a predictor of success after an amputation. J Bone Joint Surg Am 70:203–207, 1988.