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Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers Long-term follow-up

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Abstract

Background: The cause of diabetic foot ulcers is multifactorial, e.g., neuropathy and angiopathy, leading to functional disturbances in the macrocirculation and skin microcirculation. Adequate tissue oxygen tension is an essential factor in infection control and wound healing. Hyperbaric oxygen (HBO) therapy, daily sessions of oxygen breathing at 2.5-bar increased pressure in a hyperbaric chamber, has beneficial actions on wound healing including antimicrobial action, prevention of edema and stimulation of fibroblasts. The aim of the present study was to investigate the long-term effect of HBO in treatment of diabetic foot ulcers. **Methods:** Thirty-eight diabetic patients (30 males) with chronic foot ulcers were investigated in a prospective study. The mean age was 60 ± 13 years and the mean diabetes duration 27 ± 14 years. All patients were evaluated with measurements of transcutaneous oxygen tension (tcPO_2), peripheral blood pressure, and HbA_{1c}. All patients had a basal tcPO_2 value lower than 40 mmHg, which increased to ≥ 100 mmHg, or at least three times the basic value, during inhalation of pure oxygen. Seventeen patients underwent 40–60 sessions of HBO therapy, while 21 patients were treated conventionally. The follow-up time was 3 years. **Results:** 76% of the patients treated with HBO (Group A) had healed with intact skin at a follow-up time of 3 years. The corresponding value for patients treated conventionally (Group B) was 48%. Seven patients (33%) in Group B compared to two patients (12%) in Group A went to amputation. Peripheral blood pressure, HbA_{1c}, diabetes duration, and basal values of tcPO_2 were similar in both groups. **Conclusions:** Adjunctive HBO therapy can be valuable for treating selected cases of hypoxic diabetic foot ulcers. It seems to accelerate the rate of healing, reduce the need for amputation, and increase the number of wounds that are completely healed on long-term follow-up. Additional studies are needed to further define the role of HBO, as part of a multidisciplinary program, to preserve a functional extremity, and reduce the short- and long-term costs of amputation and disability.

Keywords: Hyperbaric oxygen (HBO) therapy; Diabetic foot ulcers; Transcutaneous oxygen tension (tcPO_2); Diabetic angiopathy

1. Introduction

Nonhealing foot ulcer is a common and expensive complication in diabetic patients and may lead to amputation. Almost 50% of all amputations not due to trauma are performed in diabetic patients (Boulton, Connor, & Cavanagh, 1994). The three most common causes of amputations are ischemia, infection, and retarded wound healing (Boulton et al., 1994; Larsson & Apelqvist, 1995). Retarded wound healing is related to impaired oxygenation of the skin as well as impaired cellular function secondary to hyperglycemia (Boulton et al., 1994; Hehenberger, 1997; Kalani, Brismar, Fagrell, Östergren, & Jörneskog, 1999; Tooke, 1989) The processes involved in ulcer healing are increased oxygen demanding thus a sufficient supply of blood is of great importance. Disturbances both in the macro- and microcirculation may cause local relative ischemia leading to impaired oxygen supply to the ulcer area.

Treatment of diabetic foot ulcer includes improvement of microcirculation of the skin; that is treatment of edema, anemia, and off-loading. In patients with ischemia due to advanced arterial insufficiency, the prognosis is poor without vascular reconstruction or angioplasty (Kalani et al., 1999; McNeely et al., 1995).

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Hyperbaric oxygen (HBO) therapy is a medical treatment in which a patient breathes 100% oxygen (O_2) inside a pressurized treatment chamber. It increases blood and tissue oxygen content in hypoxic tissues, which may help maintain cellular integrity and function. Intermittent HBO may help in salvaging marginally perfused tissues. It also improves (a) infection control due to enhanced mobility and bacteria-killing ability of leukocytes, (b) granulation tissue formation due to stimulation of fibroblast proliferation and collagen synthesis, and (c) microcirculation due to edema reduction and angiogenesis (Hunt & Pai, 1972; Knighton, Silver, & Hunt, 1981). It is used to treat a variety of infected, hypoperfused, and hypoxic problem wounds including chronic diabetic foot ulcers (Cianci & Hunt, 1993) and selected cases of limb-threatening foot lesions with microvascular ischemia (Faglia et al., 1996).

The present study was undertaken to investigate the long-term effect of adjunctive HBO therapy in the treatment of chronic foot ulcers in diabetic patients with peripheral hypoxia.

2. Research design and methods

Thirty-eight diabetic patients with chronic foot ulcers and local hypoxia were investigated from 1991 to 1995. Characteristics of the patients are shown in Table 1. Chronic foot ulcer and local ischemia were defined as ulcer duration > 2 months and transcutaneous oxygen tension (tcPO_2) < 40 mmHg, respectively. The mean age was 60 ± 13 years, and the diabetes duration was 27 ± 14 years. All patients were investigated by angiography and evaluated by vascular surgeons. Because of the extensive distal nature of the vascular disease and/or an increased operative risk, these patients were not eligible for reconstructive vascular surgery or angioplasty. All patients were treated with insulin. The inclusion of the first 14 patients, seven patients in each group, was randomized. Inclusion of patients in this study was stopped due to lack of availability to HBO therapy during 2 years before restarting. The remaining patients were then included in a nonrandomized way, depending on HBO availability. The regional board of ethics approved this study.

Table 1
Characteristics of 38 diabetic patients all with neuropathy, chronic foot ulcers, and local hypoxia

	HBO therapy	Conventional therapy	*P* value
n	17	21	
Sex (M/F)	12/5	18/3	
Age (years)	54 ± 14	65 ± 11	.01
IDDM/NIDDM	11/6 (65/35%)	9/12 (43/57%)	< .05
Diabetes duration (years)	28 ± 12	26 ± 17	ns
Toe pressure (mmHg)	48 ± 18	54 ± 31	ns
tcPO_2 basal (mmHg)	22 ± 12	25 ± 10	ns
tcPO_2 during O_2 inhalation	198 ± 135	185 ± 88	ns
HbA_{1c} (%)	7.1 ± 1.5	7.3 ± 1.4	ns
Ulcer area at baseline (mm^2)	1077 ± 1528	449 ± 924	.03
Smokers/nonsmokers	4/13	6/15	ns

Data are *n* or means ± S.D.

2.1. Peripheral blood pressures and tcPO_2 measurements

The patients were asked to refrain from smoking and coffee for at least 2 h before the investigations. TcPO_2 and peripheral blood pressures were measured in the supine position after an acclimatization period of 20 min. The room temperature was kept between 22 and 24 °C.

TcPO_2 was measured by an electrochemical transducer (oxykapnomonitor, SMK 363; Hellige, Freiburg im Breisgau, Germany), which was fixed to the skin with double-sided adhesive rings and contact liquid supplied by the manufacturer. The measuring site was cleaned carefully by a disinfection solution (chlorhexidin spirit). The skin oxygen partial pressure was determined by measuring the oxygen reduction current by means of a measuring cell. To increase the permeability of the skin to oxygen molecules at the measuring site, the transducer was heated to 44 °C (Huch, Huch, Arner, & Rooth, 1973). The calibration period was at an average of 10 min, and the tcPO_2 signal was continuously recorded on paper. A reference value was determined by placing the transducer on the chest at the right side in the subclavicular region (Franzeck, Talke, Bernstein, Golbranson, & Fronek, 1982). Thereafter, the transducer was placed on the dorsum of the foot in the first intermetatarsal space.

When a constant tcPO_2 value was obtained, after 10 min, the patient began to inhale pure oxygen for 10 min via a plastic box placed over the patient's head. The box had an O_2 inflow at one side and an air outflow at another side, and was isolated around the patient's neck to prevent inflow of outside air into the box.

Included in the study were patients with tcPO_2 value < 40 mmHg, which increased to $\geq$ 100 mmHg or at least three times the basic value during inhalation of pure oxygen.

All blood pressures were measured in the supine position after 20 min of rest. Systolic and diastolic arm blood pressure (mmHg) were measured by the Riva Rocci method. Systolic toe blood pressure was assessed by recording the pressure (mmHg) in a miniature cuff placed around the base of the great (mmHg) toe. Laser Doppler fluxmetry was used to show when blood flow started during cuff deflation from suprasystolic values (Påhlsson et al., 1996).

2.2. Patient care and HBO treatment

All patients were treated as outpatients according to a program developed by the foot care team (diabetologist, diabetic nurse, podiatrist, orthotist), with regular visits every 4–6 weeks. The patients had been referred due to chronic nonhealing foot ulcers.

Foot ulcers were assessed using an ulcer and a foot protocol; ulcer area and depth, signs of infection (edema, erythema, fluid discharge), signs of ischemia (foot pulses, necrosis), and signs of neuropathy (dry skin, decreased sensation using monofilament 10 g, decreased vibration sensation using fork) were documented. At the time for inclusion in the study, cultures were taken and appropriate antibiotics were used in all 38 patients until the ulcer was healed or significantly improved and no signs of infection were present, since prophylactic antibiotic treatment has been shown to reduce the frequency of wound infections compared to no prophylaxis at all (Moller & Krebs, 1985; Sonne-Holm et al., 1985). None of the patients had deep infection or full-thickness gangrene. All patients were treated with nonweight-bearing protective shoes, orthosis, improvement of metabolic control, blood pressure, and nutrition. Regular control of off-loading was performed. In all patients, the affected foot was hypoxic defined as tcPO_2 < 40 mmHg, but because of the extensive distal nature of the disease or in combination with an increased operative risk, these patients were not eligible for reconstructive vascular surgery or angioplasty.

Patients were included in the study if the foot ulcers did not heal in spite of the treatment program. Seventeen of 38 patients underwent 40–60 sessions of HBO therapy and continued the same treatment program as did patients in the control group. The daily treatment sessions were given at a pressure of 250 kPa, equivalent to 15 m H_2O, in an acrylic monoplace chamber (model 2500B, Sechrist Industries, Anaheim, CA) pressurized with 100% oxygen, allowing the patient to breathe without mask or hood. Pass-troughs allowed continued intravenous therapy and monitoring when needed. The length and frequency of treatment sessions were 90 min and five times a week, respectively. The first four patients underwent 40 sessions of HBO, the remaining 13 patients underwent 60 sessions.

3. Results

Characteristics of the two groups of patients either treated with HBO ($n = 17$), or conventionally ($n = 21$), are shown in Table 1. The mean ulcer area at baseline was significantly greater in HBO group as compared to conventional group (1077 ± 1528, 449 ± 924 mm^2, $P = .03$; Table 1). Type 1 diabetes was slightly more common in HBO group (65%) compared to the conventional group (43%) and the mean age of patients treated with HBO was significantly lower than the mean age of patients treated conventionally (Table 1). Diabetes duration, toe blood pressure, mean HbA_{1c} (HbA_{1c} reference value: < 5.2%) and tcPO_2 at dorsum of the foot, before and during O_2 inhalation, were similar in both groups.

At the end of the follow-up time (3 years), 13 of 17 patients (76%) in the HBO group had healed with intact skin and two patients (12%) were amputated below the knee (Table 2). The corresponding results in the conventional treatment group were 10 patients of 21 who healed (48%) and 7 patients (33%) were amputated below the knee (Table 2). During the follow-up time, two patients in the HBO group and three patients in conventional treatment group died, and the remaining one patient in the conventional group showed improved ulcer healing.

The mean healing time of the foot ulcers in the HBO group and the conventional group was 15 ± 7 and 15 ± 4 months, respectively ($P = .8$, range 3–30 and 8–18 months, respectively). Three of those four patients (75%) who underwent only 40 sessions of HBO healed with intact skin within 9 months (range 3–9 months), as compared to 79% of those who got 60 sessions. The remaining one patient died due to progressive heart failure 5 months after inclusion in the study.

There were totally nine patients who showed an impaired ulcer healing and were amputated during the follow-up time. There were no significant differences in tcPO_2 and toe blood pressure in these patients (24.0 ± 10.4 and 42.2 ± 29.5, respectively) as compared to those 23 patients who healed with intact skin (25.6 ± 9.6 and 56.1 ± 24.6), ($P = .7$ and $P = .2$, respectively). The mean tcPO_2 value during oxygen inhalation was significantly higher in patients who healed ($n = 23$, 234 ± 110 mmHg) as compared to those who were amputated ($n = 9$, 142 ± 65; $P = .03$). The nine patients who were amputated 61 ± 38 weeks (range 13–124) from baseline all had deteriorated with progressive gangrene with or without infection (Table 3).

The causes of death in two patients in the HBO group were multiorgan failure in one case and progressive heart failure in the other, and none of them occurred during the time of HBO therapy. In the conventional group, two patients died of cerebral infarction and one patient of progressive heart failure after an acute myocardial infarction.

Table 2
Characteristics of nine patients who were amputated

Patient	1	2	3	4	5	6	7	8	9
Treatment (HBO/conventional)	HBO	HBO	Conventional	Conventional	Conventional	Conventional	Conventional	Conventional	Conventional
Age (years)	71	43	45	57	65	63	72	66	62
Diabetes duration (years)	4	33	31	48	28	16	55	14	20
tcPO_2 (mmHg)	31	8	34	30	28	21	25	16	11
Toe pressure (mmHg)	40	70	21	90	40	45	100	100	15
Ulcer area at baseline (mm^2)	49	1250	680	203	605	225	524	345	90
Ulcer duration at baseline (weeks)	18	24	16	26	19	21	16	17	15
Time from inclusion to amputation (weeks)	105	55	124	16	56	78	13	66	32

Table 3
Characteristics of 23 patients who healed with intact skin and 9 patients who were amputated at the end of follow-up time

	Healed ($n=23$)	Amputated ($n=9$)	P value
Age (years)	58 ± 15	60 ± 10	ns
IDDM/NIDDM	13/10 (57/43%)	6/3 (67/33%)	
Diabetes duration (years)	30 ± 15	26 ± 14	ns
Toe pressure (mmHg)	56 ± 25	42 ± 30	ns
tcPO_2 basal (mmHg)	26 ± 10	24 ± 10	ns
tcPO_2 during O_2 inhalation (mmHg)	234 ± 110	142 ± 65	.03
HbA_{1c} (%)	6.9 ± 1.2	7.9 ± 1.7	ns
Ulcer area at baseline (mm^2)	817 ± 1425	416 ± 466	ns
Smokers/ nonsmokers	6/17	2/7	

Data are n or mean ± S.D. Patients have been divided into two groups according to ulcer.

Two patients experienced side effects; one patient developed cataract which was assumed to be caused by HBO treatment, and one patient had a problem with pain in ears which was relieved after local treatment with a decongestant.

4. Discussion

Our results are in agreement with other prospective randomized or comparative studies showing positive effects of adjunctive HBO therapy on ulcer healing and reduction of amputation rate in diabetic patients with chronic foot ulcer and local hypoxia.

Previously published controlled, prospective trials have focused on patients with diabetic foot infections and partial foot gangrene. Baroni et al. (1987) reported that 89% (16 of 18 patients) healed in the HBO group, whereas only 10% (1 of 10 patients) healed in the control group. In a study involving 80 patients, Oriani et al. (1990) reported a 96% healing rate and a 5% amputation rate for the HBO group, versus 66% and 13% in the control group, respectively. In another small prospective study on 10 patients, Zamboni, Wong, Stephenson, and Pfeifer (1997) found significant improvement in healing in the HBO group versus the control group. Faglia et al. (1996) in the best controlled, prospective, and randomized trial so far published on 68 patients, showed an 8.6% amputation rate in patients treated with HBO versus 33.3% in controls ($P < .016$). Among patients with Wagner's Class IV lesions (gangrene of the toes or forefoot), the HBO group had a major amputation rate of 9.1% (2 of 22 patients) versus 55% (11 of 20 patients) for the control group ($P = .002$). In a comparative study by Faglia et al. (1998) on 115 patients, HBO reduced major amputations significantly.

In contrast to the studies above, none of the patients in our study had full-thickness gangrene or deep infection. Furthermore, a rather long follow-up time was chosen to investigate the long-term effects of HBO therapy, since the healing of diabetic foot ulcers, especially in patients with peripheral arterial occlusive disease, may take several months, or sometimes years (Apelqvist, Ragnarson-Tennvall, & Larsson, 1995) with risk for recurrence and/or new ulcers when one has healed. In the present study, 38 diabetic patients with chronic foot ulcer and local hypoxia at the foot, defined as tcPO_2 < 40 mmHg, and a significant rise in tcPO_2 during inhalation of pure oxygen, were investigated. The patients received adjunctive HBO therapy or continued conventional therapy, and were followed up for 3 years. HBO therapy was tolerated well and only two patients experienced mild side effects, which shows that HBO is a safe treatment method.

The number of amputations was lower and more patients healed with intact skin in the HBO group. The time to healing was similar in both the HBO and control groups in spite of more Type I diabetes and a greater ulcer area at baseline in patients in the HBO group, indicating that HBO therapy accelerated ulcer healing in these patients. On the other hand, the age was significantly different between the two groups, and the younger HBO-treated group of patients may have had a better wound-healing potential than the older group of patients.

An effective ulcer healing process demands adequate supply of oxygen to the ulcer area. Measurements of tcPO_2 is a noninvasive method reflecting local arterial blood flow and skin oxygenation (Hauser, Klein, Mehringer, Appel, & Shoemaker, 1984). TcPO_2 can be used to determine the severity and clinical progression of peripheral arterial occlusive disease (Quigley & Faris, 1991), and values < 40 mmHg are associated with poor ulcer healing in diabetic patients (Brakora & Sheffield, 1995; Kalani et al., 1999; White & Klein, 1989). Measurement of tcPO_2 during inhalation of pure oxygen or HBO exposure has been used to select patients for HBO therapy (Brakora & Sheffield, 1995; Campagnoli & Oriani, 1992). A significant rise in tcPO_2 predicts the beneficial effect of HBO therapy (Brakora & Sheffield, 1995; Campagnoli & Oriani, 1992).

HBO has properties of a drug. The hyperbaric chamber (pressure vessel) can be looked upon as a syringe through which HBO is injected, i.e., more O_2 is dissolved in the blood. When more O_2 is supplied than the tissue demand, O_2 pressure in the blood rises and O_2 can diffuse further into the tissues. Intermittent reoxygenation, across the barriers created by edema and poor perfusion, can maintain cellular integrity and function which may help salvage marginally perfused tissues.

Wound healing is O_2-dependent and rate-limited by its availability at the cellular level, e.g., collagen formation. HBO stimulates ulcer healing by increasing blood oxygen content, edema reduction, enhanced mobility, and bacteria-killing ability of leukocytes, stimulation of collagen synthesis, neovascularization with improvement in capillary density, and granulation tissue formation (Hunt & Pai, 1972; Knighton et al., 1981; Sheffield, 1988). New evidence suggests that HBO also stimulates one or more of a variety of growth factor-mediated wound-healing processes, e.g., fibroblast proliferation (Hehenberger, Brismar, Lind, & Kratz, 1997).

Microcirculation and oxygenation improves after a series of HBO treatments. New capillaries are formed in selected ischemic or poorly perfused wounds. It has also been shown that tcPO_2 values are permanently increased in diabetic patients who benefit from HBO therapy (Faglia et al., 1996) but in this study tcPO_2 measurements were not repeated. Thus, HBO therapy is a good complement to ulcer care program for a subgroup of patients but it cannot replace such a program. The possibility for reconstructive vascular surgery or angioplasty must be examined and, if possible, the patient has to undergo vascular surgery before consideration for HBO therapy.

Effective utilization of HBO therapy also requires appropriate selection of patients and then careful monitoring of progress. Our study suggests that diabetic patients with local hypoxic foot ulcer (tcPO_2 <40 mmHg) not eligible for vascular surgery may benefit from HBO therapy when tcPO_2 value increases to >100 mmHg and/or at least three times basal value during inhalation of pure oxygen.

However, measurement of tcPO_2 during oxygen breathing in the hyperbaric chamber may be a more accurate clinical approach to evaluate patients for HBO therapy, to evaluate oxygenation, and hence, vascular status, and to predict ulcer healing (Campagnoli & Oriani, 1992), but this method was not used in this study. Additionally, we did not evaluate tcPO_2 at the vicinity of a wound but rather standardized in the first intermetatarsal space on the dorsum of the foot.

The total costs of diabetic foot ulcers and amputations are high in both a short- and long-term perspective, and costs increase with ulcer severity (Apelqvist, Ragnarson-Tennvall, Larsson, & Persson, 1995; Apelqvist, Ragnarson-Tennvall, Persson, & Larsson, 1994). In addition, and not surprisingly, quality of life is significantly reduced in patients with ulcers or after major amputations (Ragnarson-Tennvall & Apelqvist, 2000). The cost of 40–60 HBO treatments were 60–90,000 SEK in 97 prices, approximately one fourth to one tenth of the cost of an amputation (Apelqvist, Ragnarson-Tennvall, Larsson, & Persson, 1995; Apelqvist et al., 1994).

Our results with long-term follow-up, and those of others, indicate a potential for HBO therapy in the treatment of selected hypoxic diabetic foot ulcers. It seems to accelerate the rate of healing, reduce the need for amputation, and increase the number of wounds that are completely healed on long-term follow-up. Additional studies are needed to further define the role of HBO, as part of a multidisciplinary program, to preserve a functional extremity with quality of life, and reduce the short- and long-term costs of amputation and disability.

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