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The Role of Hyperbaric Oxygen Therapy in Ischaemic Diabetic Lower Extremity Ulcers: a Double-blind Randomised-controlled Trial

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Objective: *ischaemic lower-extremity ulcers in the diabetic population are a source of major concern because of the associated high risk of limb-threatening complications. The aim of this study was to evaluate the role of hyperbaric oxygen in the management of these ulcers.*
Method: *eighteen diabetic patients with ischaemic, non-healing lower-extremity ulcers were recruited in a double-blind study. Patients were randomly assigned either to receive 100% oxygen (treatment group) or air (control group), at 2.4 atmospheres of absolute pressure for 90 min daily (total of 30 treatments).*
Results: *healing with complete epithelialisation was achieved in five out of eight ulcers in the treatment group compared to one out of eight ulcers in the control group. The median decrease of the wound areas in the treatment group was 100% and in the control group was 52% ($p = 0.027$). Cost-effectiveness analysis has shown that despite the extra cost involved in using hyperbaric oxygen, there was a potential saving in the total cost of treatment for each patient during the study.*
Conclusion: *hyperbaric oxygen enhanced the healing of ischaemic, non-healing diabetic leg ulcers and may be used as a valuable adjunct to conventional therapy when reconstructive surgery is not possible.*

Key Words: Hyperbaric oxygenation; Peripheral arterial diseases; Wound healing; Diabetes mellitus; Randomised controlled trial.

Introduction

At anytime about 5–7% of the diabetic population are estimated to have a lower-extremity ulcer of varying severity.[1,2] These ulcers are a source of major concern because of the high risk of developing serious limb threatening complications.[3,4] Several well-accepted risk factors predispose diabetic patients to ulceration. The most important include peripheral arterial disease (PAD) and peripheral neuropathy.[5,6] PAD is a major contributing factor in 60% of the lower-extremity ulcers in diabetic patients.[1,7] In these ulcers, bacterial infection is common and wound hypoxia is well documented.[8–10]

Hyperbaric oxygen therapy has been demonstrated to have an antimicrobial effect and to increase oxygenation of the hypoxic wound tissues. This enhances the neutrophil killing ability, stimulates angiogenesis, and enhances fibroblasts activity and collagen synthesis.[11–14]

Despite the seriousness of complications arising from lower-extremity diabetic ulcers, the international medical community has not accepted hyperbaric oxygen therapy as an adjunctive treatment because of the poor quality of reports supporting its use and the relatively high cost of the treatment.[15,16] In view of this we conducted a double-blinded, randomised-controlled study to examine the role of hyperbaric oxygen therapy in the treatment of diabetic lower-extremity ulcers in patients with PAD. The study objective was to determine whether hyperbaric oxygen, as compared to control, could have any therapeutic effect on these ulcers. Secondary objectives included the influence of hyperbaric oxygen on quality of life measures and a limited economic evaluation of its use.

Patients and Methods

Participants

Diabetic patients presenting to Hull Royal Infirmary with ischaemic lower-extremity ulcers were recruited

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if they had an ulcer more than 1 cm and less than 10 cm in maximum diameter which had not shown any signs of healing, despite optimum medical management for more than 6 weeks since presenting. Occlusive arterial disease was confirmed by an ankle-brachial pressure index <0.8 (or great toe-brachial pressure index <0.7 if calf vessels were incompressible). Acceptable metabolic control of their diabetes was judged by glycated haemoglobin level of less than 8.5%. All patients underwent diagnostic angiography as part of their vascular assessment. Decision on vascular intervention was made by the clinician responsible for the care of each patient. In general, the four consultant vascular surgeons in Hull are relatively aggressive in relation to distal revascularisation. Patients for whom vascular surgery, angioplasty or thrombolysis was planned were excluded. The study was approved by the local ethics committee and informed consent was obtained from all patients. The trial started in April 1999 and ended in April 2001.

Intervention and randomisation

Patients were randomly assigned either to receive hyperbaric 100% oxygen (treatment group) or hyperbaric air (control group). The randomisation was performed using sealed envelopes and the randomisation code was only known to the chamber operator. All patients, their carers and medical assessors were blinded to the treatment. The treatment in both groups was given in a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute (ATA) for 90 min daily, 5 days per week, totalling 30 sessions. Decompression time was extended to 20 min to avoid giving oxygen supplement during decompression to the control group without compromising their safety. Medical management was optimised and equivalent for all patients in both groups. All patients regularly attended a specialised multi-disciplinary clinic comprising a diabetic physician, a vascular surgeon, a chiropodist and a specialist nurse, for at least 6 weeks before recruitment into this study and throughout the study treatment and follow up period. Wound care was standardised for all patients and included off-loading, aggressive debridement and dressing which ensured that a moist wound environment was maintained. Antibiotic therapy was given if there were clinical signs of infection.

Evaluation of response to treatment

Any patient with more than one ulcer had only one of the ulcers selected at random to be included in the study. The primary outcome was the ulcer surface area measurement. Ulcers were copied into a transparent sheet and then transferred into a digital image. Surface area was calculated using a special software program (SigmaScan®). Complete healing was documented if complete epithelialisation of the ulcer was evident. Ulcer assessment also included measuring ulcer depth and looking for clinical signs of infection. Quality of life was measured using the generic form SF-36 and Hospital Anxiety and Depression Scale (HAD scale).

Patients were assessed at baseline, after 15 and after 30 treatments, and 6 weeks later. Two more follow-up visits were performed at 6 months and 1 year. The primary objective of this study was to determine whether there was a significant reduction in the ulcer size at six weeks after the end of the intervention.

Cost effectiveness analysis

The mean total cost of visits for ulcer dressing per patient during the 1 year follow-up period of the study in the control group was compared with the respective cost in the treatment group in addition to the cost of hyperbaric oxygen treatment per patient and the cost of dealing with any complications arising from the treatment. The estimated costs of an out-patient hospital visit for ulcer dressing is £58 (figure obtained from NHS Executive 2000 costs for the U.K.). The standard amount charged by the Hull Hyperbaric Unit for hyperbaric oxygen therapy per patient is £100 for each session.

Statistical analysis

Sample size was based on similar work on venous ulcers.[17] Data analysis was on an intention-to-treat basis. A p-value of less than 0.05 was considered to be significant. When distribution did not satisfy the parametric assumptions, non-parametric tests were used. The analyses were performed using SPSS version 9.0.

Results

Of 25 patients screened, five were excluded because they did not conform to inclusion criteria and two patients refused to take part in the study. None of the patients were suitable for straightforward vascular reconstructive surgery. Eighteen patients were

Table 1. Patients' characteristics. OHG (oral hypoglycaemic therapy), COPD (chronic obstructive pulmonary disease), GTPI (great toe-brachial pressure index), $TcPO_2$ (transcutaneous oximetry).

Group	Treatment	Control	p value
Age (years)*	72 ± 12.6	70 ± 6.6	NS
Sex (male:female)	2:1	1:2	NS
Diabetes duration* (years)	13 ± 9.9	10 ± 6.3	NS
OHG	4/8	3/8	NS
Insulin therapy	4/8	5/8	NS
Retinopathy			
Background	7/8	8/8	NS
Proliferative	1/8	0/8	NS
Smokers	1/8	2/8	NS
Neuropathy* (Biothesiometer)	47 ± 16.2	55 ± 13.7	NS
SVS classification: Grade 5	8/8	8/8	NS
GTPI*	0.47 ± 0.24	0.44 ± 0.3	NS
Foot $TcPO_2$* (mmHg)	46 ± 15	43 ± 19	NS
COPD	1/8	2/8	NS
Cardiac failure	2/8	2/8	NS
Haemoglobin* (g/dL)	12.7 ± 1.2	12.5 ± 1.7	NS
Serum albumin* (g/L)	37 ± 2.8	38 ± 2.6	NS
Serum urea* (mmol/L)	8.5 ± 3.8	7.6 ± 2.9	NS
Body mass index*	26 ± 7	29 ± 4	NS
Previous angioplasty	0/8	1/8	NS
Previous bypass surgery	2/8	3/8	NS
Previous amputation			
Minor	1/8	2/8	NS
Major	0/8	0/8	NS
Previous ulcers	3/8	4/8	NS

SVS: Society of Vascular Surgery.
* Results as mean ± SD.

randomised into one of two groups (nine treatment and nine control). Two patients withdrew during the course of the study (one in the control group required urgent vascular intervention and one in the treatment group dropped out for personal reasons). The protocol was strictly followed throughout the study. All patients received their treatment as outpatients and no adverse events related to hyperbaric therapy were recorded during the study period. Patients' characteristics are shown in Table 1.

At 6 weeks follow up, complete healing was achieved in five out of eight ulcers in the treatment group compared with one out of eight ulcers in the control group. The respective results at 1 year follow-up were five out of eight and 0 out of eight ($p = 0.026$, Fisher's exact). Furthermore, the median decrease of the wound areas, at 6 week follow up, in the treatment group was 100% compared with 52% in the control group ($p = 0.027$, Mann–Whitney). However, values at 6-month follow-up were 100 and 95% respectively (Table 2).

Patients in both the treatment and control groups showed a significant improvement in the depression score in the HAD Scale ($p = 0.011$ and 0.023 respectively, Wilcoxon) while only the control group had a significant reduction in their anxiety score ($p = 0.042$, Wilcoxon). The SF-36 has detected a significant improvement in the general health and vitality domains in the oxygen group ($p = 0.012$ and 0.018 respectively, Wilcoxon) but there was no significant improvement in the other domains in both groups and no significant difference between the two groups overall. In summary, hyperbaric oxygen did not produce any significant improvements in quality of life measures greater than those seen in patients in the control group as measured by the SF-36 and HADS.

Table 2. Ulcers description and outcome.

Group	Treatment	Control	p value
Ulcer size (mm^2)*	106 (12–823)	78 (18–866)	NS
Ulcer depth (mm)*	2.3 (0.5–4)	1.6 (0.5–4)	NS
Wagner Grade I	0	1	NS
Wagner Grade II	8	7	NS
Signs of infection	3/8	2/8	NS
Ulcer duration (months)	6 (2–18)	9 (3–60)	NS
Ulcers healed:			
At 6 weeks	5/8	1/8	NS
At 6 months	5/8	2/8	NS
At one year	5/8	0/8	$p = 0.026$
Reduction in ulcer size			
At 6 weeks	100% (34–100)	52% ((−29)–100)	$p = 0.027$
At 6 months	100% ((−206)–100)	95% (0–100)	NS
Major amputation	1	1	NS
Minor amputation	1	0	NS

* Results as median and (range).

During the follow up period, the mean number of visits for dressing of the study ulcer was 33.75 (±62) per year per patient in the treatment group and 136.5 (±126) per year per patient in the control group. The mean total cost per patient per year for ulcer dressing visits was £1972 in the treatment group and £7946 in the control group. Since the cost of the entire hyperbaric oxygen treatment course per patient was £3000 there was a significant potential cost saving by using adjunctive hyperbaric oxygen amounting to an average of £2960 for each patient treated.

Discussion

Wound healing is a physiological response to tissue damage consisting of a series of events culminating in repair. However, patients with diabetes exhibit different biological responses to those classically described in the healing process. Multiple factors are involved in non-healing lower-extremity ulcers in diabetic patients. Ischaemia, oedema, infection, poor glycaemic control, autonomic and sensori-motor neuropathy, and abnormal haemodynamics all impede the normal healing process.[18–22] Wound hypoxia is well

documented in non-healing wounds, representing the strongest risk factor in those patients.[6,10] Initial studies have explained the role of oxygen as a metabolite involved in many basic functions. Studies by Hunt *et al*. and Knighton *et al*. have shown that oxygen stimulates angiogenesis and enhances fibroblasts activity and leukocyte function.[11,13,14] Siddiqui *et al*. have concluded that hyperbaric oxygen also acts as a stimulus to signal transduction of specific pathways important for wound healing.[23] Abidia *et al*. have demonstrated that in diabetic patients with PAD, cutaneous microvascular reflexes are normalised under hyperbaric oxygen conditions.[24]

Although there are limited data to support most treatments for diabetic ulcers, six approaches are supported by clinical trials or well-established principles of wound healing; off loading, debridement, appropriate dressing, management of infection, vascular reconstruction, and amputation as appropriate.[25,26] Adjunctive medical therapies include normalisation of blood glucose, control of co-morbid conditions, treatment of oedema, and nutritional therapy. However, despite advances in medical and surgical care, 14–24% of diabetic patients with lower-extremity ulcers will require an amputation.[3,4,27]

The role of oxygen supplement in those patients with peripheral arterial disease is less clear.[15,16] Most vascular surgeons would accept that improving tissue perfusion with reconstructive vascular bypass surgery or angioplasty is an early priority.[18] However, on many occasions such procedures are inappropriate, impossible or have already failed. Several centres in the world use hyperbaric oxygen as an adjunctive treatment for such patients. Nevertheless, few therapies in medicine have encountered such controversy for so long as has hyperbaric oxygen for chronic wounds. The lack of sufficient clinical data is partly because of the difficulty and expenses required in running clinical trials in this area, the different aetiology of different wounds, and the relatively small number of patients presenting to centres equipped with hyperbaric chambers.

Faglia *et al*. has reported, in a randomised controlled trial, a significant reduction in major amputation rate in diabetic patients undergoing hyperbaric oxygen therapy compared with controls.[28] The majority of patients in this study had advanced ischaemia resulting in gangrenous lesions. The control group received best medical care and the primary endpoint was lower-extremity amputation. Kalani *et al*. investigated the long-term benefit of hyperbaric oxygen therapy in patients with diabetic foot ulcers. Improved healing and reduced amputation rate was reported. This study was also not blinded and the control group received best medical care.[29] Several other authors have reported favourable results in healing of diabetic ulcers by using hyperbaric oxygen.[30,31] A success rate of 70–95% was reported, however, these studies were heavily criticised in their methodology and have been largely ignored by the medical community. These studies had several aspects in common: all were non-blinded; none were randomised and the control groups were of patients unsuitable for the treatment or those who refused the treatment; and none had a placebo control group.[16,32]

In our study, we targeted diabetic patients with ischaemic non-healing ulcers in their lower-extremities in whom vascular intervention was impossible or considered inappropriate. We have demonstrated that hyperbaric oxygen treatment at 2.4 ATA for 90 min had significantly reduced the ulcer size in the lower-extremities of diabetic patients with PAD compared with those receiving pressurised air. The response was clinically obvious after 15 treatments and became statistically significant after 30 treatments. Patients in the control group also had a reduction in their ulcers size albeit at a much slower rate compared to the treatment group. Eventually the reduction in ulcer size in the two groups was comparable at 6 month follow-up of those patients. Nevertheless, despite the reduction in ulcer size in the control group, all of these ulcers remained unhealed at 1 year follow up (Table 2). Consequently, the difference in complete healing between the two groups was statistically significant at 1 year follow-up. Follow-up of these patients was discontinued after 1 year because the authors felt that any difference observed between the two groups beyond one year cannot be confidently attributed to the hyperbaric oxygen therapy, and is more likely to be due to natural progression of peripheral arterial disease. In agreement with previous studies in patients with Wagner grade II ulcers, this study did not show any difference in major or minor amputation rate between the two groups.

The ulcer healing progress during the study period shown in Figure 1 indicates that the benefit of hyperbaric oxygen persisted after discontinuing the treatment. Such an effect, suggests that hyperbaric oxygen has instigated a process that allowed healing to continue in an enhanced rate later under normal conditions. In the absence of significant changes in transcutaneous oxygen values of the lower limb at the end of the study (Table 3), this effect appears to be mediated through the pharmacological effects of oxygen, i.e., a signal transduction mechanism.

Improvements in the ulcer size in the control group were slightly better than those reported in the literature for patients of similar age and extent of

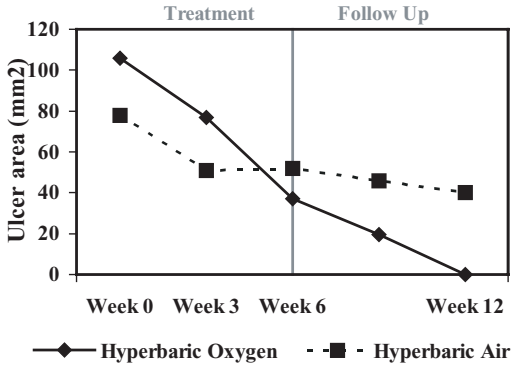

Fig. 1. Ulcer progress during the treatment and follow up period.

Table 3. Pre and Post study $TcPO_2$ (transcutaneous oximetry) values. Results as Mean ± SD.

Foot $TcPO_2$ (mmHg)	Treatment	Control	*p* value
Breathing air			
Pre-study	46 ± 15	43 ± 19	NS
Post-study	49 ± 19	47 ± 20	NS
Breathing 100% Oxygen			
Pre-study	97 ± 36	80 ± 44	NS
Post-study	94 ± 37	75 ± 40	NS

arterial disease. A possible explanation is that the control group received an amount of oxygen during the intervention equivalent to breathing 50% oxygen on sea level. However, this is generally considered to be insufficient to produce any clinical effect in this group of patients. Another explanation is the participation effect. This combines the intensity of the care given to those patients together with the patients' motivation and the placebo effect of hyperbaric therapy. A positive psychological impact of hyperbaric therapy in this study was observed in the control group. When questioned at the end of the study, the majority of patients in both groups believed they received the active treatment (6/8 in the treatment group and 5/8 in the control group), while the rest could not guess which treatment they were given, and none of the patients believed they were in the control group. A significant improvement in the depression scores in both groups and in the anxiety score in the control group was also observed. Such an effect could be explained by the social outing provided by participating in the study for an age group that is otherwise confined to home with little other activity. It could also be explained by the motivation provided by enrolling in this study. The lack of significant difference between the groups and in particular the lack of improvement in physical functioning, as assessed by the SF-36, in the treatment group despite the majority having had their ulcers healed was surprising, and suggests that their physical functioning was not mainly limited by the ulcers. The frequent existence of other co-morbid conditions such as intermittent claudication, arthritis, and cardiac problems may explain this observation. Moreover, generic quality of life measures were used in this study. A disease-specific quality of life measure may have been more appropriate in detecting benefit achieved with ulcer healing.

In this study a difference between the groups, although not statistically significant, in sex ratio and body mass index (BMI) was noted. We are not aware of any impact that gender has on healing but BMI is pertinent to the healing process. The mean difference in BMI was three, which in this study translates to 8 kg in weight. Although this may be a contributing factor, we do not feel that this on its own could explain the significant difference in healing between the groups.

Cost-effectiveness is very important in treatment selection. The cost of hyperbaric oxygen therapy varies from one place to another and depends on set up costs, ongoing costs and the number of patients being treated in the unit. In Hull, patients are charged £100 per session. A limited economic analysis in this randomised controlled trial has shown that despite the extra cost of the treatment, hyperbaric oxygen has potentially reduced the total cost by an average of £2960 for each patient treated during the 1 year period of the trial, simply by reducing the number of visits required for ulcer dressing. We accept that this is crude and not an accurate figure and also that saving will vary between units.

Other potential problems in relation to hyperbaric oxygen therapy include compliance with the treatment, claustrophobia, and various complications such as oxygen toxicity and decompression illness. Because of the length of the treatment full commitment from the patients is required which may represent a problem for patients in full-time employment. In our study, patient compliance was more than 95% and no complications were observed. The extra time used during decompression in this study ensured increased safety for the study groups.

In conclusion, the results of this first double-blinded, randomised-controlled trial have shown that hyperbaric oxygen has the potential to enhance healing of ischaemic diabetic lower-extremity ulcers and is cost-effective. Although our results indicate that hyperbaric oxygen should be considered as an adjunct in the management of these ulcers, the results must be viewed with caution and viewed as preliminary because of the small sample used. This study demonstrates the need for a large multi-centre trial to confirm the results.

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