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Evaluation of the Role of Hyperbaric Oxygen Therapy in the Treatment of Diabetic Foot Ulcers: a Prospective Comparative Study

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Abstract

Aim/Objectives: This prospective study aims to assess the efficacy of hyperbaric oxygen therapy in diabetic foot ulcers in relation to standard wound care.

Methods: This was a single centre prospective study conducted from January 2007 to March 2015 by the department of surgery. In total, 240 consenting patients with foot ulcers of at least two weeks duration were randomized with the help of a random number generator into two groups each comprising 120 patients: the HBOT group (to receive hyperbaric oxygen therapy along with standard wound care) and the ASD group (to receive standard wound care only). The six-week treatment phase was followed by a six-week follow-up phase. Wounds were monitored using the Bates-Jensen Wound assessment scale. For all statistical analysis, a p-value of less than 0.05 was taken to indicate a significant difference.

Results: Of the 240 patients, 164 were male and 36 female. The duration of diabetes was not statistically significant (p-value 0.707). In the study group, the wounds of 22 (88) (73.3%) patients healed in less than eight weeks (i.e. 56 days), vs. only 4(16) (13.3%) patients in the control group, which was statistically significant (p value <0.001)

Conclusion: This study further supports and recommends HBOT for the management of diabetic foot ulcers as there is marked increase in the rate of wound healing as compared to standard wound care and dressings alone.

Key words: *Diabetes; foot ulcers; hyperbaric oxygen therapy; antiseptic dressing*

Introduction

Depending on the aetiology of diabetes mellitus (DM), factors contributing to hyperglycaemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden both on the individual with diabetes and on the healthcare system [1]. In India, DM is the leading cause of adult blindness, end-stage renal disease (ESRD), peripheral neuropathy and non-traumatic lower extremity amputations. Among diabetes mellitus-related complications, foot ulceration is the most common, affecting approximately 15% of diabetic patients during their lifetime [2]. This can be attributed to several social and cultural practices such as barefoot walking, inadequate facilities for diabetes care and education, and poor socioeconomic conditions [3]. Limb amputation has a major impact on the individual, not only in terms of body image distortion, but also with regard to loss of productivity, increased dependency, and costs of treating foot ulcers if patients require inpatient care [4].

This prospective study aims to assess the efficacy of hyperbaric oxygen therapy (HBOT) in diabetic foot ulcers in relation to standard wound care with antiseptic dressing (ASD)

Materials and methods

Study design: This was a single centre prospective study conducted from January 2007 to March 2015 by the department of surgery. Diabetic patients presenting to the surgical emergency or outpatient department with foot ulcers of at least two weeks duration were included in the study. The

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protocol was approved by the ethical review board of the institute. Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki 1975.

Participants: The patients were selected from those attending the surgical outpatient and emergency department at the hospital. The age of the patients varied from 23 to 73 years with most of the patients falling within the age range of 51-60 years. Inclusion criteria were patients aged ≥ 18 years with type I or II diabetes mellitus, and foot lesions classed as Wagner grades of 2, 3 or 4 without signs of healing for at least two weeks. According to the Wagner Classification System, these grades are defined as follows:

Grade 2: Deep ulcer, penetrating down to the ligaments and muscle, but no bone involvement or abscess formation

Grade 3: Deep ulcer with cellulitis or abscess formation

Grade 4: localized gangrene

Exclusion criteria were impending urgent amputation due to ongoing or exacerbated infection, exposed calcaneum bone with no prospect of weight-bearing potential, major large vessel disease and deep venous thrombosis, history of chemotherapy with bleomycin, current candidates for vascular surgery or angioplasty, up to 3-month history of vascular surgery or angioplasty, and women who are pregnant or breast feeding. In addition, wounds excluded from the study were Wagner grade 0: no ulcer in a high-risk patient; grade 1: superficial ulcer involving the full skin thickness but not underlying tissues; and grade 5: extensive gangrene involving the whole foot. The following medical conditions were also excluded: clinical depression, severe dementia, claustrophobia, seizure disorder, active asthma, severe COPD, previous thoracic surgery, previous spontaneous or trauma induced pneumothorax, history of severe congestive heart failure with left ventricular ejection fraction less than 20%, unstable angina, chronic sinusitis, deafness, acute or chronic otitis media or major ear drum trauma, severe kyphoscoliosis, severe arthritis, and morbid obesity.

Methods: Two hundred and forty consenting patients were randomized with the help of random number generator into two groups, each comprising 120 patients: the HBOT group (to receive hyperbaric oxygen therapy along with standard wound care) and the ASD group (to receive standard wound care only). The 6-week treatment phase was followed by a 6-week follow-up phase.

Biochemical diagnosis of diabetes was made according to the American Diabetes Association guidelines. The pathological and biochemical blood tests were conducted in the hospital laboratory using computerized auto-analyzers. All patients had tests for complete blood count, fasting and post-prandial blood sugar level, renal function test, serum electrolytes, and serum albumin; they also underwent urine routine examination, radiography of the chest and of the diseased limb to check for osteomyelitis and demineralization, and bilateral lower limb arterial and venous Doppler. Ear, nose and throat (ENT) reference was sought before starting HBOT to assess the patients for the risk of barotrauma. The Hyperbaric Oxygen Machine BARA-MED smooth-ride installed in the department of anaesthesia was used. Ulcer debridement, as well as amputation and skin grafting was performed as and when required. Monitoring of the wound was based on the Bates-Jensen wound assessment score (BJWAS) [5]. BJWAS includes 13 characteristics with a score of 1-5: size, depth, edge, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin colour surrounding wound, peripheral tissue oedema, peripheral tissue induration, granulation tissue, and epithelialisation. This score ranges from 13-65.

In addition to the standard wound care given during the treatment phase to both groups (described below), the HBOT group received one 60-minute daily session of HBOT at 2.5 ATA O_2 pressure for 10 days every two weeks for six weeks. After the 6-week treatment phase, patients were followed up for a further six weeks. The control group received only standard wound care during the treatment phase, which included maintenance of optimal blood glucose level by insulin therapy, debridement of the ulcer, antiseptic dressing, administration of antibiotics to control infection, adequate nutrition, pressure-relief in areas of the foot that are most susceptible to weight bearing and amputation. After six weeks of standard wound care, patients were followed up for another six weeks. Assessment of the wound in terms of size, edges, depth, undermining, necrotic tissue type and amount, exudate type and amount, skin colour around the wound area, peripheral tissue oedema and induration, granulation tissue, and epithelisation was made every week both at treatment and follow-up phase.

Statistical analysis: Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentages. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t-test for two groups and ANNOVA for three or more groups. Categorical variables were analysed using either the chi-square test or Fischer's exact test. For all statistical analysis, a p-value of less than 0.05 was taken to indicate a significant difference.

Results

General characteristics: The study involved 240 subjects, 164 of whom were male and 76 female. In the HBOT group, 84/120 were male and 36/120 female while in the ASD group, 80/120 were male and 40/120 female. The age

of the patients varied from 23 to 73 years with the majority falling within the age range of 51-60 years (64 patients in the HBOT group and 56 in the ASD group) followed by the 41-50 years age range (36 patients in the HBOT group and 40 patients in the ASD group).

Duration of diabetes: Diabetes duration was classified as less than 10 years or more than 10 years (table 1), and was not statistically significant (p-value: 0.707).

HbA1C level: There was no statistically significant difference between the two groups with respect to HbA1C level (p-value: 0.734) (table 1).

Foot deformities: An observation was made of the various presentations of foot deformities (table 2). There was no statistically significant difference (p-value: 0.841).

Bates Jensen wound assessment score: This score was used to evaluate the progression of the ulcer (tables 3 and 4). The wounds receiving HBOT showed early healing when compared to standard wound care. Table 3 shows that the difference in BJWAS was not statistically significant at day 1 (p-value: 0.05). However, as the days of HBOT progressed, the difference started to become statistically significant (p-value: < 0.001).

Healing was enhanced in almost all patients in the HBOT group as compared with the ASD group. As shown in table 5, wound healing in 88 (73.3%) patients in the HBOT group was achieved in less than eight weeks, i.e. 56 days, as opposed to just 16 (13.3%) patients in the ASD group ; this difference was statistically significant (p-value: <0.001). Similarly, it took 24 (20%) patients in the HBOT group more than eight weeks for the wound to heal in contrast to 100 (83.3%) patients in the ASD group.

Along with enhanced healing, HBOT also improved the duration of hospital stay. As shown in table 5, the maximum stay of duration for 80 (66.7%) patients in the HBOT group was less than four weeks as opposed to just 16 (13.3%) patients in the ASD group; this difference was statistically significant (p-value: <0.001). The number of patients whose hospital stay exceeded four weeks was 32 (26.7%) in the HBOT group and 100 (83.3%) in the ASD group.

Skin grafting was required in only 12(10%) patients in

Table 1. *Comparison of various parameters between HBOT and ASD group.*

Parameters	HBOT group(n=120)		ASD group(n=120)		P-value
Duration of diabetes	frequency	percent	frequency	percent	
<10 years	20	16.7%	12	10%	0.707
>10 years	100	83.3%	108	90%	
HbA1C level					
<=6.5	4	3.3%	0	0	0.734
6.51-7.5	40	33.3%	36	30%	
7.51-8.5	68	56.7%	72	60%	
>8.5	8	6.7%	12	10%	
Lower limb arterial and venous colour Doppler					0.706
Normal	108	90%	100	83.3%	
Abnormal	12	10%	20	16.7%	

Table 2. *Comparison of foot deformities between study group and control group.*

Foot Deformity	Study Group		Control Group		P-Value
	Frequency	%	Frequency	%	
No Deformity	76	63.3%	68	56.7%	0.841
Clawed toes	24	20.0%	28	23.3%	
Hammer toes	12	10.0%	16	13.3%	
Plantar flexed metatarsal	8	6.7%	8	6.7%	
Charcot foot	0	0.0%	0	0.0%	
Total	120	100%	120	100%	

Table 3. *Comparison of Bates Jansen Wound assessment score between study group and control group at different points.*

Bates Jansen wound assessment score	Study Group	Control Group	P-Value
	Mean ± SD	Mean ± SD	
Day 1	47.30 ± 5.43	50.20 ± 5.78	0.050
Day 14	41.40 ± 6.28	46.87 ± 7.40	0.003
Day 28	34.23 ± 7.36	43.70 ± 8.46	<0.001
Day 42	26.93 ± 8.18	39.86 ± 9.52	<0.001
Day 49	19.29 ± 8.04	36.41 ± 11.21	<0.001
Day 56	15.79 ± 7.78	34.21 ± 10.97	<0.001
Day 63	15.11 ± 6.20	31.72 ± 10.46	<0.001
Day 70	14.79 ± 5.25	29.45 ± 10.23	<0.001
Day 77	14.04 ± 3.05	28.10 ± 10.21	<0.001
Day 84	13.86 ± 2.53	26.62 ± 10.20	<0.001

the HBOT group vs. 68 (56.7%) in the ASD group, which was statistically significant (p-value: 0.001). HBOT enhanced wound healing in such a way that the requirement of skin grafting was significantly reduced. The prevention of amputation was not statistically significant. However, the number of amputations was higher in the ASD group: 12 (10%) patients in the HBOT group vs. 32 (26.7%) in the ASD group.

Discussion

The number of people with diabetes worldwide was estimated at 131 million in 2000. This figure is projected to increase to 366 million by 2030. The number of cases in India are predicted to more than double by 2030, from 31.7 million as reported in 2000 to 79.4 million in 2030 [6].

Among persons diagnosed as having diabetes mellitus, the lifetime risk of developing a foot ulcer is estimated to be 15% [7]. Based on recent studies, the annual population-based incidence ranges from 1.0% to 4.1% [8] and the prevalence ranges from 4% to 10%, which suggests that the lifetime incidence may be as high as 25% [9,10]. Lower extremity disease, including peripheral arterial disease, peripheral neuropathy, foot ulceration, or lower extremity amputation, is twice as common in diabetic persons

Table 4. *Number of patients with Bates Jensen Wound Assessment Score of 13 in two groups.*

Bates Jansen wound assessment score (13)	Study Group (n=120)		Control Group (n=120)		P Value
	Frequency	%	Frequency	%	
Day 1	0	0.0%	0	0.0%	-
Day 14	0	0.0%	0	0.0%	-
Day 28	0	0.0%	0	0.0%	-
Day 42	4	3.3%	0	0.0%	1.000
Day 49	16	13.3%	16	13.3%	1.000
Day 56	88	73.3%	16	13.3%	<0.001
Day 63	100	83.3%	16	13.3%	<0.001
Day 70	100	83.3%	16	13.3%	<0.001
Day 77	100	83.3%	16	13.3%	<0.001
Day 84	100	83.3%	16	13.3%	<0.001

Table 5. *Comparison of duration for healing, hospital stay and mortality between HBOT and ASD groups.*

duration for healing	HBOT group		ASD group		P value
	Frequency	percent	Frequency	percent	
<8 weeks	88	73.3%	16	13.3%	<0.001
>8 weeks	24	20%	100	83.3%	
Hospital stay					
< 4 weeks	80	66.7%	16	13.3%	<0.001
> 4 weeks	32	26.7%	100	83.3%	
Deaths	8	6.7%	4	3.3%	

compared with non-diabetic persons, and it affects 30% of diabetic persons above 40 years of age [11].

Considering the high risk of amputation in patients with diabetes and the epidemic of diabetes, it is of utmost importance to conduct a randomised multicentric controlled trial to evaluate the efficacy of various adjunctive therapy for treatment and further progression of diabetic ulcer. In this study, we tried to evaluate the efficacy of HBOT in the treatment of diabetic ulcer.

The mean age of patients presenting with diabetic foot ulcer in our study was 51.30 ± 7.83 in the HBOT group and 48.03 ± 7.49 in the ASD group. The youngest patient in the HBOT and ASD group was aged 34 and 33 years, respectively and the oldest patient 66 and 60 years, respectively. The productive age group (30-60 years) was 93.3 % and 100 % in the HBOT and ASD group, respectively. Sporadic qualitative research suggests that diabetic foot ulceration has a profound social impact with patients reporting stigma, social isolation, loss of social role, and unemployment [12], which is comparable with other Indian studies. In most Indian and Asian studies [13,14,15], the mean age of presentation was the third and fourth decade of life. Compared with western studies [16,17], we found that patients in the Indian setup are at risk of developing ulcer at an early age.

The sex distribution noted in our study was similar in both groups. The HBOT group comprised 84(70%) males and 36(30%) females while the ASD group included 80(66.7%) males and 40(33.3) females. Although most studies show a male predilection for diabetic complications like ulceration, its incidence among the female population appears to be on the rise.

The duration of diabetes plays an important role in the development of diabetic ulcer and other complications. In our study, it was seen to be more than 10 years for 100 (83.3%) patients in the HBOT group and 108 (90%) patients in the ASD group. The longer the duration of diabetes, the greater the risk for developing foot ulcer. After 10 years of diabetes, the risk of ulcer is significantly increased.

Similarly, HbA1c levels are also important in determining the risk for diabetic ulcer. In our study, 68 (56.7%) patients from the HBOT group and 72 (60%) from the ASD group had HbA1c levels between7.51 and 8.50. Healing slows down in cases of raised HbA1c levels, especially when they exceed 8.5. Hence, to avoid bias in our study, patients with HbA1c values >8.5 were first treated for deranged diabetes before being included in the study. The majority of studies [16,18] have demonstrated an inverse correlation between HbA1C levels and the rate of healing in diabetic wounds.

Various studies [14,15] used the wound area as a parameter to evaluate the effect of the wound in terms of wound healing after HBOT or standard wound care. We used Bates Jensen wound assessment score (BJWAS) as a tool to evaluate the efficacy of HBOT and standard wound care and also as a marker of completely healed wounds. An ideal BJWAS is 13, denoting a completely healed wound. At the end of six weeks, four patients in our study from both the study and control group had a score of 13, which was not statistically significant (p-value: 1). However, at the end of eight weeks, 88 (73.3%) patients in the HBOT group achieved a score of 13 as opposed to only 16 (13.3%) in the ASD group; this difference was statistically significant (p-value: <0.001). At the end of the follow-up phase, 100 (83.3%) patients in the HBOT group and 16 (13.3%) in the ASD group achieved a score of 13 (p-value: <0.001). To our knowledge, this is the first study to evaluate wounds using the BJWAS. In the study conducted by Abidia A et al. [15], the response to HBOT was clinically obvious after 15 treatments and became statistically significant after 30 treatments. Kaur et al. [13] reported 59.5% reduction in the wound area after HBOT and 26% after standard wound care after 30 days of therapy. Kalani M et al. [18] reported the mean healing time of foot ulcers in the HBOT group and the conventional group as 15±7 and 15± 4 months, respectively. Most studies [16,19,20] have reported a significant acceleration of wound healing with HBOT. However, this is the only study to report a statistically significant difference in the rate of healing; among the 14 patients who underwent 20 sessions of HBOT, only in two patients did ulcers heal after four weeks; this may be due to the low number of HBOT sessions [17]. When compared with other studies, the rate of healing was faster and better in our study, which could possibly be ascribed to our enrolling only patients with controlled blood sugar values and better compliance with HBOT sessions. Adopting the BJWAS as a standard wound assessment tool could further reduce possible errors in evaluating results of various studies and render them more comparable.

In our study, the difference in amputation rate was not statistically significant (p-value: 0.228). When compared with other studies, it was virtually similar. Faglia et al. [21] reported three subjects (8.6%) who underwent major amputation: two below the knee and one above the knee, signifying an amputation rate of 10 % in the study group vs., 26% in ASD group; this concurred with the findings of other studies [13,21].

The hospital stay of a diabetic ulcer patient is drastically reduced with HBOT. In our study, the hospital stay of 80 (66.7%) HBOT patients and just 16 (13.3%) ASD patients was less than 28 days (1 month), (p-value: <0.001). As the rate of healing improves, the duration of hospitalisation reduces, which ultimately decreases the cost of treatment. Abidia et al. [15] reported the significant potential for cost-saving with the use of HBOT as adjunctive treatment. In our study, apart from earache, no major side effects of

HBOT were noted.

In conclusion, the present study further supports and recommends HBOT for the management of diabetic foot ulcers since it shows a marked increase in the rate of wound healing as compared to only standard wound care and dressings. Furthermore, HBOT allows the patient to resume daily work sooner by decreasing the hospital stay and also improves the badly affected personal, social and professional life of the diabetic foot ulcer patient.

Ethical Approval-Informed Consent: *The protocol was approved by the ethical review board of the institute. Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki 1975.*

Conflict of Interest: *The authors declare that there is no conflict of interest.*

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