Original Article

Hyperbaric oxygen therapy as an adjuvant to standard therapy in the treatment of diabetic foot ulcers

Atit Kumar, Usha Shukla, Tallamraju Prabhakar[1], Dhiraj Srivastava[2]

Departments of Anaesthesiology and [2]Community Medicine, UPUMS, Saifai, [1]Department of Anaesthesiology, Vivekanand Polyclinic and Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Abstract

Background and Aims: Chronic diabetic foot ulcers pose a major problem because of associated limb threatening complications. The aim of the present study was to evaluate the efficacy of hyperbaric oxygen therapy (HBOT) as an adjuvant to standard therapy for treatment of diabetic foot ulcers.

Material and Methods: A total of 54 patients with diabetic foot ulcer of Wagner grade II–IV were recruited in this prospective, randomized, double blind study. Patients were randomized to receive HBOT along with standard therapy (group H; $n = 28$) or standard therapy alone (group S; $n = 26$). Patients were given 6 sessions per week for 6 weeks and followed up for 1 year. Outcomes were measured in terms of healing, and need for amputation, grafting or debridement. Parametric continuous variables were analyzed using Student unpaired *t*-test and categorical variables were analyzed using Chi square test.

Results: The diabetic ulcers in 78% patients in Group H completely healed without any surgical intervention while no patient in group S healed without surgical intervention ($P = 0.001$). 2 patients in group H required distal amputation while in Group S, three patients underwent proximal amputation.

Conclusion: The present study shows that hyperbaric oxygen therapy is a useful adjuvant to standard therapy and is a better treatment modality if combined with standard treatment rather than standard treatment alone for management of diabetic foot ulcers.

Keywords: Foot ulcer diabetic, hyperbaric oxygenation, wound healing

Introduction

Diabetes nowadays is a global health problem, producing major economic burden on patient and healthcare.[1] Out of the reported incidence, 19-35% of the diabetic ulcers are non-healing[2] and almost 10-20% progress to lower extremity amputation.[3] Hence, despite careful treatment with multiple modalities like debridement, relief of pressure and dressings, many foot ulcers remain non-healing and require new treatment strategies such as ultrasound therapy, electrical stimulation, use of growth factors, bioengineered tissues, negative wound therapy and hyperbaric oxygen therapy besides conventional therapies. In hyperbaric oxygen therapy (HBOT), patients breathes 100% oxygen for a specified period of time in a pressurized chamber at pressure higher than atmospheric pressure at sea level. It causes increased blood and oxygen content in hypoxic tissues which maintains the cellular integrity and function. It also has antimicrobial activity due to enhanced mobility and bacteriophagic activity of leukocytes. HBOT promotes granulation tissue formation due to fibroblast proliferation and collagen synthesis, and improves microcirculation due to edema reduction and angiogenesis.[4,5]

Address for correspondence: Dr. Usha Shukla,
201, Type V, New Campus, UPUMS, Saifai, Etawah - 206 130, Uttar Pradesh, India.
E-mail: ushashukla1970@gmail.com

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The present study aims to evaluate the efficacy of HBOT as an adjuvant to standard therapy and compare it to standard therapy alone on the basis of healing, need of surgical intervention and amputation as treatment of diabetic foot ulcers in patients admitted in an Indian hospital with limited resources.

Material and Methods

After getting approval from the ethical committee of the university and written informed consent, patients suffering from diabetic foot ulcers and admitted to different medical and surgical departments, underwent full clinical examination and were evaluated for potential inclusion in study. Diabetic patients more than 18 years of age and having a non-healed foot ulcer for at least 4 weeks despite standard treatment, of grade II-IV according to Wagner classification[6] and inadequate distal perfusion were included in the study. Besides the standard assessment, all patients underwent Trans-cutaneous partial pressure of oxygen ($TcPO_2$) measurement and were evaluated for any contraindication to HBOT. Patients who had untreated pneumothorax, previous history of thoracic surgery, vascular surgery, angioplasty, ear surgery, congestive cardiac failure, unstable angina, chronic sinusitis, major ear drum trauma, severe arthritis, upper respiratory tract infection, chronic obstructive pulmonary disease, convulsions, hypoglycemic episodes, or febrile state and patients on corticosteroids, amphetamine, catecholamine, or thyroid hormone were excluded from the study. Patients who were currently pregnant or were breast feeding were also excluded from the study.

$TcPO_2$ measurement- The patients were asked to refrain from smoking and coffee for at least two hours before investigations. $TcPO_2$ (Model: TMC Comi M Make: M/s Radiometer Medical Aps Denmark) was measured in supine position after acclimatization for 20 minutes. The room temperature was maintained between 21°C and 24°C. Calibration was performed before each measurement. $TcPO_2$ was measured on dorsum of the foot in the first metatarsal space, the area which was directly lying over the bones and superficial veins was avoided. The measuring site was cleaned very carefully using antiseptic solution (chlorohexedine and spirit) and an electrochemical transducer was placed and fixed over the skin using two sided adhesive rings and contact liquid supplied by the manufacturer. The transducer was heated to 42°C - 45°C, so as to cause capillary dilation, opening skin pores and by decreasing oxygen solubility enabling tissue oxygen tension to be measured. After baseline equilibration, the values of $TcPO_2$ were recorded every minute for 6-8 min while patient was breathing room air and for 6 min while patient was breathing 100% O2 and the highest values were recorded as basal and stimulated $TcPO_2$ respectively. Patients in whom the $TcPO_2$ value were 40 mm Hg and increased upto ≥100 mm Hg or at least 3 times the basal values during inhalation of 100% oxygen were included in the study.

After fulfilling the inclusion criteria, the patients were randomly allocated to the Standard treatment + HBOT (Group H) or the Standard treatment (Group S), using a permuted block randomization method with a multiple block size of 10. The HBOT technician obtained the treatment allocation through an internet, based automated randomization system. The patients and the researchers were blind to the treatment allocated to study groups while the HBOT technician, who was responsible for controlling the hyperbaric oxygen chamber, was not blinded.

Standard treatment included maintenance of optimal glucose levels, daily dressings depending on the type of wound (dry, wet or infected), simple gauze, alginate or sitosterol dressing, collagen/oxidized cellulose dressings, local debridement at bedside or in OR, along with adequate nutrition and pressure relief as well as amputation as and when indicated. Infection control was achieved by clinical follow ups and culture antibiograms of surgically obtained specimen to determine appropriate antibiotics therapy.

In the Group H, the standard therapy was supplemented with hyperbaric oxygen treatment administered at a working pressure of 2.4 ATA Abs using a Monoplace chamber (Make: Perry Baromedical Corporation, USA, Model: Sigma 34 Elite Monoplace Hyperbaric Chamber) for 90 min, while in all those patients who were randomized to Group S were kept on compressed air to 0.3 ATA and the patients remained in the chamber for the reminder of placebo treatment, breathing normally. At the end of the treatment, enhanced ventilation was administered for a very short period to stimulate surfacing and the chamber was opened. Each patient received treatment cycle of 6 sessions per week, up to a period of 6 weeks, for a total of 36 sessions. After the completion of treatment phase for 6 weeks, patients entered follow-up phase.

All patients in both the groups had the following independent variables recorded: age, gender, type of diabetes, duration of diabetes, hypertension, lipids, smoking habits, obesity, Hb (gm%), glycosylated hemoglobin states (HbA1C in gm%), $TcPO_2$(Basal and Stimulated), and grade, size and duration of ulcer. Obesity was defined as patient with body mass index (BMI) equal to or more than 29.9. Smoker was

defined as a patient who had quit smoking within two months of presentation or was a current smoker. Lipid lipoprotein levels were labeled as high if triglycerides were 180 mg% or high, cholesterol 200 mg% or high and LDL 160 mg% or higher.

Outcomes were defined as:
(1) Complete closure of wound without any surgical intervention
(2) Surgical grafting or flap was required
(3) Distal or proximal amputation was required
(4) Operative surgical debridement was done to achieve wound closure
(5) No change in wound condition.

Outcomes were observed every week during the treatment phase and first 6 weeks of follow-up phase and then at 3 months' interval for a year. Both study groups were compared with regard to wound healing, need of amputation and surgical interventions.

Ulcer, when completely covered by epithelial tissue and persistently remained so till the next visit was considered to be healed. Wagner grade IV ulcer was considered to be healed, when the gangrene had completely separated and underlying ulcer was completely covered by epithelial regenerative tissue. In case, patient required major (above ankle) amputation, the ulcer was considered as non-healed. The decision of amputation was taken by vascular surgeon if any of the criteria mentioned below was met:
(a) Persistent deep infection involving bone and tendons
(b) Ongoing risk of severe systemic infection related to wound
(c) Inability to bear weight on the affected limb and pain causing severe disability.

With an alpha error of 0.05 and power of 85%, we hypothesized that HBOT treatment had eight times better outcome than standard treatment. A sample size of 27 per group was calculated using power and sample size calculator, version 3.0.34. The study proposed to recruit participants for 6-month period and each participant was followed for a period of 12 months. Thus after rounding the figure, we increased the sample size to 30 patients in each group. Data were analyzed using intent to treat analysis. All the continuous data was analyzed using unpaired Student *t* - test while all the categorical data was analyzed using Chi-square test. Statistical analysis was conducted using the SPSS (version 24.0). *P* value of less than 0.05 was considered to be statistically significant.

Results

In the present study, 65 participants who were fulfilling the inclusion criterion were registered, five patients were excluded hence 60 patients were randomized to 2 groups with 30 patients in each group. As regard to group H, 28 patients completed 36 sessions, while in group S, 26 patients completed 36 sessions [Figure 1]. No patient in any group underwent open vascular surgery in the affected limb during the 1 year follow-up.

The demographic characteristics of the patients in the two study groups are shown in Table 1. There were 20 men and 8 women in Group H, and 19 men and 7 women in Group D. There were 12 patients with Type 1 and 16 with Type 2 diabetes in Group H, and 12 with Type 1 and 14 with Type 2 diabetes in Group S.

No patient in group S healed without any surgical intervention versus group H, in which 22 (78%) patients healed completely without undergoing any surgical intervention. Mean healing time in group H was significantly shorter than in group S [Table 1]. In group S, 26 (100%) patients required either debridement in operating room and amputation for healing of the ulcer, while in group H, 6 (21%) patients required these surgical interventions.

With regard to distal vs. proximal amputation, 12 patients underwent distal amputation while proximal amputation was

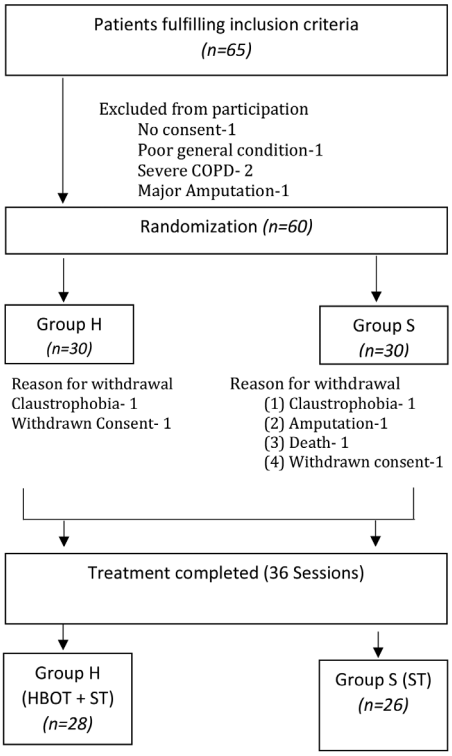

Figure 1: Flow diagram of patients' inclusion and study procedure

performed in 3 (11%) patients in Group S. In group H, 2 (7%) patients underwent distal amputation while proximal amputation was not done in any patient [Table 2].

Discussion

Diabetic patients develop foot ulcers because of multiple factors. Advanced age, male gender, duration of diabetes >10 years, obesity, peripheral neuropathy, peripheral vascular disease, poor glycemic control along with foot trauma increase the likelihood of development of foot ulcers in diabetic patients.[7-9] Wound hypoxia represents to be the strongest risk factor for non-healing wound in diabetic patient.[10] The risk of amputation is higher in diabetic patients who have such type of non-healing ulcer than non-diabetic population.

Treatment modalities used in diabetic foot ulcer can be common treatment options like debridement (mechanical, surgical, autolytic, enzymatic and biological by means of maggots), pressure relief/offloading techniques (shoes, half shoes, sandals, insoles, in-shoe orthosis and socks) and various dressings and topical agents (hydrocolloids, hydrogels, foam, films and silver impregnated dressings) are used for wound closure and reepithelialization. Newer modalities for advanced care include use of growth factor (platelet derived growth factor, fibroblast growth factor, vascular endothelial growth factor, insulin like growth factor, epidermal growth factor and transforming growth factor b) bioengineered skin (Apligraft, dermagraft and oasis), electrical stimulation, ultrasound therapy and negative pressure wound therapy.[4] Multiple modalities are practiced to promote healing in diabetic ulcer patients but HBOT may prove to be useful when these modalities fail or are unavailable[11]

Hyperbaric oxygen therapy involves the administration of 100% O_2 to patients at pressure 2.5-3 times higher than atmospheric

Table 1: Comparison of patient characteristics in the two groups

Variable	Group H (*n*=28)	Group S (*n*=26)	*P*
Age (years)	58.4±10.1	56.9±11.1	0.6
Durationof diabetes (yrs)	14.4±5.9	15.0±4.9	0.982
Hypertension	13	14	0.566
High Lipids levels‡ (mg/dl):	21	19	0.872
Smoking habits- Smoker§: Non smoker	25:03	17:09	0.03
Obesity	18	14	0.4635
Hb (gm%)	10.5±2.3	10.7±1.9	0.7289
Glycosylated Hb (gm%)	8.4±1.8	8.1±2.5	0.6131
TcPO2 (mm Hg)			
(i) Basal	23±10	24±9	0.701
(ii) Stimulated	188±133	185±86	0.922
Wageners' grades: II: III: IV	10:10:8	9:9:8	0.9845
Ulcer Size (cm^2)	2.9±1.5 (0.5-38)	3.0±2.8 (0.6-40)	0.869
Ulcer duration (Months)	8±2.1 (3-40)	9±2.9 (3-39)	0.152
Healing time (Months)	8±2	10±2	<0.001

Results are presented as number for categorical data or mean±SD for continuous numeric data. Tcpo2¶ - Trans-cutaneous partial pressure of oxygen. Smoker§: Active smokers or those who quit within two months of presentation. High lipids levels‡=Triglycerides ≥180 mg/dl, cholesterol ≥200 mg/dl and low density lipoprotein ≥160 mg/dl.

Table 2: Ulcer grades and outcome (*n*=54)

Outcome / Variable	Wagener's ulcer Grade II (*n*=19)		Wagener's ulcer Grade III (*n*=19)		Wagener's ulcer Grade IV (*n*=16)	
	Group H (*n*=10)	Group S (*n*=9)	Group H (*n*=10)	Group S (*n*=9)	Group H (*n*=8)	Group S (*n*=8)
Healed* (*n*=22)	10	0	7	0	5	0
Graft/Flap† (*n*=2)	0	0	0	0	2	0
Distal amputation‡ (*n*=14)	0	3	1	6	1	3
Proximal amputation§ (*n*=3)	0	0	0	0	0	3
Debridement‖ (*n*=11)	0	6	2	1	0	2
No change¶ (*n*=2)	0	0	0	2	0	0
P	<0.001		0.005		0.006	

Results are presented as number for categorical data. Outcomes: Healed: Complete closure of ulcer without any surgical intervention, Graft/Flap†: Graft or flap closure required, Distal amputation‡: Amputation distal to metatarsophalengeal joint, Proximal Amputation§: Amputation proximal to metatarsophalengeal joint, Debridement‖: operative surgical debridement (in the operating room) to achieve closure. No change¶: Failure to heal*

pressure. The efficacy of HBOT as a treatment of diabetic foot ulcers has been advocated by several clinical trials. Londahl *et al.*,[12] Tiaka *et al.*,[13] and Kranke *et al.*[14] found that complete healing of the index ulcer occurs in 50% patients in hyperbaric group compared to 29% patients in conventional treatment group. We also observed the same findings, which could be attributed to the fact that hyperbaric O_2 stimulates angiogenesis and increases the fibroblast proliferation and collagen production, leading to an increase in tensile strength of the wound.[15-17] The increase in O_2 tension produced by HBOT, which persists for several hours after therapy, is responsible for angiogenic properties of HBOT.[14] The high oxygen tension (≥30-40 mmHg) produced by HBOT, causes superoxide enzymes to act more rapidly on both aerobic and anaerobic bacteria thereby demonstrating the bactericidal and bacteriostatic effects of HBOT.[18] Also, HBOT has been shown to have synergistic effects with many antibiotics like aminoglycosides, trimethoprim, nitrofurantoin and sulphisoxazole.[19] In addition, during hyperbaric oxygen therapy, hyperoxic vasoconstriction occurs which leads to reduced capillary pressure and increased vascular permeability resulting in decreased transcapillary fluid transfer and increase in extravascular fluid resorption which reduces lower extremity edema.[18] The intermittent reoxygenation across the barrier formed by edema and poor perfusion maintains cellular integrity and function which can help in salvage of marginally perfused tissue. Hyperbaric O_2 causes reduced platelet aggregation, improved tissue microcirculation, and diminished metabolic disturbances. These properties along with increased dissolved O_2 in plasma lead to better oxygenation of hypoxic tissue, where red blood cells cannot reach.[20]

An adequate supply of oxygen at ulcer area is required for an effective ulcer healing. Local arterial blood flow and skin oxygenation can be non-invasively reflected by measuring $TcPO_2$.[21] Quigley and Farris[22] showed that $TcPO_2$ can be used to determine the severity and clinical progression of peripheral arterial occlusive disease and values <40 mmof Hg are associated with poor ulcer healing in diabetic patients. Measurement of $TcPO_2$ during inhalation of pure oxygen in HBOT was used to select the patient for HBOT and a significant rise in $TcPO_2$ is a good predictor of beneficial effects of HBOT. Niinikoski *et al.*[23] found that transcutaneous partial O_2 pressure can be useful in predicting which patient will be benefited, if given hyperbaric O_2 therapy. Kalani *et al.*[24] concluded that $TcPo_2$ measurement at dorsum of foot is a better predictor for healing of chronic diabetic foot ulcer than TBP as it has high prediction value in reflecting regional macrocirculation and nutritive skin microcirculation. Measurement of $TcPO_2$ during inhalation of pure O_2/HBO exposure can be used to select patients for HBO treatment.

In our study, we found that need for amputation is less in patients who had baseline values of $TcPO_2$ >22 mm Hg and whose $TcPO_2$ raised to 3 times of baseline values after therapy with hyperbaric oxygen [Table 3], however no statistically significant difference ($P = 0.102$) was noted as the sample size was small thus it is recommended that a bigger study with large sample size is required to make more precise recommendations. To grade the severity of diabetic foot ulcers, Wagner's classification[6] is commonly used although this is criticized for lacking sensitivity and specificity, for not taking into consideration difference between neuropathic and vasculopathic diabetic foot ulcer. Efforts are made to provide guidelines regarding the use of HBOT, many clinicians rely strongly on clinical acumen rather than $TcPO_2$ measurement to determine that a patient can be benefited from HBOT. We used both to predict and grade the severity of ulcer and the potential benefit a patient can get from the use of HBOT. In the present study, ulcers were graded according to Wagener's classification and both the treatment groups were similar as regard to ulcer grades. However, there was a high prevalence of smokers in HBOT group which is a harmful risk factor for wound healing. Inspite of this risk factor, the patients in Group H fared well than those in group S showing the beneficial effect of HBOT on wound healing.

With regard to amputation in present study, no major amputation took place in HBOT group while three patients in group S had to undergo proximal amputations although the present study was not powered to detect the superiority of HBOT over standard treatment. All the amputations which took place in our study, had Wagner's grade IV ulcers. Our results are similar to other studies which demonstrated the beneficial effects of HBOT in preventing amputation.[5,24]

In group H, complete healing of the ulcer was significantly faster as compared to group S which is similar to the observations made by Fagila *et al.*,[25] Stoekenbroek *et al.*[20] and Londahl *et al.*[12] that HBOT causes improved rate of complete healing at one year follow up. Liu *et al.*[26] in a meta-analysis have shown that rate of healing and quality of life is improved and

Table 3: Distribution of patients with or without amputation on the basis of TcPO2 measurements

Parameter	Non Amputated	Amputated	*P*
TcPO2¶ >22 (mmHg) (*n*=31)	24	7	0.102
TcPO2 <22 (*n*=23)	13	10	

Results are presented as number for categorical data. Tcpo2¶ - Transcutaneous partial pressure of oxygen.

risk of major amputation is reduced in diabetic patient when we give hyperbaric oxygen therapy. We also found the similar results as Liu *et al.*, with reduced amputation ratio in HBO group H than standard therapy group S. Margolis *et al.*[27] concluded that hyperbaric O2 therapy neither improves the likelihood of wound healing nor prevents amputation in diabetic patients with foot ulcer having contrary outcome to present study attributable to different methodology between two studies.

Fagila *et al.*[25] showed that in diabetic patients who are benefited from HBOT therapy have permanently increased $TcPO_2$ values but in present study $TcPO_2$ measurements were not done in follow up period. To more accurately evaluate the patients for HBO therapy, oxygenation and hence vascular status and to predict ulcer healing measurement by$TcPO_2$ during oxygen breathing in hyperbaric chamber is more accurate clinical approach[28] but this method was not used in present study. Also, $TcPO_2$ was not measured in the vicinity of foot ulcers rather it was standardized to be measured in the dorsum of foot in first metatarsal space. We did not examine the relationship of complications and cost of different therapeutic interventions in regard to outcome. Hence, more clinical trials and studies with larger patient base are needed to be conducted to overcome these draw backs and biases.

In conclusion, the present study observed that hyperbaric oxygen therapy is useful adjuvant to conservative standard therapy in healing of diabetic foot ulcer with limited side effects and relative safety and is better treatment modality if combined with standard therapy rather than standard treatment alone.

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Conflicts of interest
There are no conflicts of interest.

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