Prospective study in the role of hyperbaric oxygen therapy in diabetic foot wound healing-an experience in an Indian public hospital

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The Journal of Diabetic Foot Complications, 2017; Volume 9, Issue 1, No. 4, Pages 21 - 30

Abstract:

The study aims to assess the benefits of Hyperbaric Oxygen Therapy (HBOT) for treating chronic non-healing diabetic ulcers. This prospective randomized controlled study included 50 patients in the study group who received HBOT and standard treatment and 50 patients in the control group who received only standard treatment. Standard treatment included medications, wound dressing, and operative procedures like debridement, graft, and flap closure. Only diabetic patients older than 18 years old with chronic non-healing ulcers for more than three months were included in the study. Infection recovery rate in the study group was 79.06% (34 out of 43) and 47.61% (20 out of 42) in the control group. Five patients in the study group and seven patients in the control group had non-infected ulcers. Healing rate in the study group was 64.58% (31 out of 48) and 2% (1 out of 49) in the control group. Amputations were performed in 20.83% (10 out of 48) and 63.26% (31 out of 49) patients in the study group and control group, respectively. Operative procedures were carried out in 27% patients (13 out of 48) in the study group and 87.75% patients (43 out of 49) in the control group. The average hospital stay for patients in the study group was 30.68 days and 52.4 days for those in the control group. These results were statistically significant ($p<0.05$), favoring the study group. HBOT offers a significant advantage over the traditional methods for infection and healing recovery rates, and significantly helps in reducing the number of amputations, operative procedures, and treatment costs. We believe there is a continuing role for HBOT for diabetic foot ulcers as an adjunct to standard therapy.

Key words: Diabetic Foot, Hyperbaric Oxygen Therapy, Non-healing Ulcer

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INTRODUCTION

Diabetes is a global health crises, which has major economic consequences for patients, their families, and society.

Over the past few decades there has been an alarming rise in the prevalence of diabetes. The International Diabetes Federation (IDF) Atlas reported that the number of people with diabetes was approximately 366 million in 2011, and by the year 2030 this number will rise to 552 million people. It also estimated that approximately 80% of people with diabetes live in low and middle income countries, which are designated as the developing economics in the world.[1]

The prevalence of diabetes in India is particularly noticeable, since the number of people with diabetes in India is exceedingly high compared to any other country in the world. Per the latest IDF Atlas, there were more than 65 million people with diabetes in India.[2]

Among the complications from diabetes, foot complications are a major cause of hospital admission for diabetic persons. The presence of foot complications increases health care costs and poses a heavy socioeconomic burden, both on patients and the nation. A majority of diabetic patients develop foot ulcer, gangrene, and abscess during the course of their illness, which may require long-term hospitalization and amputation.

Diabetic foot problems can be caused by the following:

1. The foot is the most vulnerable part of body, susceptible to injury, infections, and patient neglect.
2. The foot is the site of neuropathy and ischemia.
3. Foot infections are polymicrobial in nature, and to avoid complications they must be appropriately diagnosed and treated.

Diabetic foot ulcer management is multifactorial and is based on a comprehensive clinical examination and an understanding of the underlying etiology.[4,5] Common treatment options in patients with diabetic foot ulcers include mechanical and surgical debridement, pressure relief/off-loading, and the use of various dressings and topical agents designed to facilitate wound closure and promote re-epithelialization. Advanced care modalities for the treatment of diabetic foot ulcers include the use of growth factors, bio-engineered tissues, electrical stimulation, ultrasound therapy, negative pressure wound therapy, and hyperbaric oxygen therapy.

Hyperbaric oxygen therapy (HBOT) is defined as breathing 100% oxygen at pressures higher than normal atmospheric pressure at sea level in a hyperbaric chamber. (1 ATM is 14.7 pounds per square inch (PSI), 1 kg per square centimeter, or 760 mm Hg.) Since oxygen has an important role in the physiology of wound healing, HBOT is a useful adjunct in the treatment of diabetic foot ulcers[6,7] because it helps increase tissue oxygen tensions to levels that promote wound healing, limit edema, and destroy certain anaerobic bacteria.

The aim of the study was to assess the benefits of HBOT for treating non-healing chronic diabetic ulcers.

The objectives were to assess the effect of:

1. HBOT on healing of diabetic foot ulcers
2. Total number of amputations
3. Total operative procedures
4. Curing of infection
5. Hospital length of stay

MATERIALS AND METHODS

This was a prospective randomized control study that compared the effect of chronic wound healing when treated with and without HBOT.

From July 2013 to October 2015, 100 diabetic subjects, consecutively hospitalized in our diabetology unit for foot ulcer, underwent our diagnostic and therapeutic protocol and evaluated for potential inclusion in the investigation. In addition to receiving standard medical assessment, each patient was evaluated to determine whether HBOT was contraindicated. Diabetic patients were considered eligible if they were at least 18 years old and if they had a foot wound that was present for at least three months despite appropriate local systemic wound care. All patients were assessed by a vascular surgeon at the time of inclusion, and only patients with adequate distal perfusion or non-reconstructable peripheral vascular disease were included in the study.

All the patients were further evaluated 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 treatment plus HBOT group. We assigned patients using a random number table and allocated them to the treatment groups according to a predetermined sequence where consecutively enrolled patients corresponding to an even random number received standard treatment and those corresponding to an odd random number received standard treatment plus HBOT. We continued this process until we had 50 participants in each treatment group.

All patients gave their informed consent. One subject randomized for HBOT refused the treatment, and one subject expired four days after admission due to acute stroke.

One subject, randomized for the non-HBOT, died of myocardial infarction three days after admission. All three subjects were excluded from the analysis of the results. Of the subjects, 48 underwent HBOT and 49 did not.

Diagnostic and Therapeutic Protocol

Upon hospital admission the patient's lesions were classified according to the Wagner Classification. In our clinical practice, diabetic subjects with full-thickness gangrene (Wagner grade 4) or abscess (Wagner grade 3) were admitted to the hospital. Subjects with less-deep ulcers (Wagner grade 2) were also admitted if the ulcer was large and infected and showed a defective healing in three months.

All patients were examined for diabetic

retinopathy (fundus oculi by ophthalmologist), albumin excretion rate (mg/24 h, the average of three 24-h collections), renal impairment (creatinine >1.3 mg/dL), arterial hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg or antihypertensive therapy), coronary artery disease (CAD) (CAD-resting electrocardiogram and Bmode echocardiography), obesity (BMI >24 kg/m2 for women, >25 kg/m2 for men), dyslipidemia (triglyceride 180mg/dL or higher), and cholesterol (200mg/dL or higher and low-density lipoprotein 160mg/dL or higher or on hypolipidemic therapy). On admission and at discharge, glycosylated hemoglobin levels (HbAlc high-pressure liquid chromatography, normal values 4.4-6%) were measured. Smokers were defined as current, active smokers or those who quit within two months of presentation. Specimens of the foot lesion, after decontamination and debridement followed by curettage, were collected for aerobic and anaerobic culture, and for antimicrobial susceptibility testing to antibiotics. Susceptibility testing to topical antimicrobial agents was also performed according to a standardized protocol set up in our microbiology laboratory. X-rays were taken of both feet and legs to discover medial arterial calcifications and bone abnormalities.

The ankle-brachial blood pressure ratio (ankle-brachial index [ABI]) was measured by Doppler continuous wave technique. Initially, aggressive debridement was performed, and the wound was dressed. Dressings were changed at required intervals. After the collection of swabs from the wound, patients were given empirical antibiotic treatment. This was modified if necessary according to the sensitivity tests. Blood glucose levels were optimized with insulin. The feet were protected from uncontrolled mechanical stresses and subjected to off-loading.

Patients then underwent HBOT. The antibiotic therapy was continued during the hospital stay until the culture exam was negative. After discontinuation of the antibiotic therapy, re-culturing to assess the cure was performed every two days, for a total of three times. An optimized metabolic control was pursued either with subcutaneous insulin administrations or oral hypoglycemic agents. The decision to carry out a major amputation was taken by the consultant surgeon who was unaware of whether the HBOT was administered or not. Follow-up visits were fixed at six months and one year following discharge. The study ended when the patient was healed, the foot was amputated, or there was no change. Statistical significance was defined at 5% (p value <0.05).

Hyperbaric Oxygen Therapy

In the group randomized for HBOT, the patients breathed pure oxygen in a mono place hyperbaric chamber, pressurized with air, with a soft helmet. The chosen pressure in our study was 2.5 absolute atmosphere (ATA) for a period of 90 minutes for each session for five out of seven days in a week, with an off at the weekend.

Patients included in the study were those who:

1. Were 18 years or older and who were suffering from Type 1 or 2 diabetes mellitus
2. Had chronic non-healing ulcers (ie, more than six weeks and non-healing for more than three months)
3. Had ulcers of a Wagner's grade of 2, 3, or 4

Patients excluded from the study were those who:

1. Were on chemotherapy or suffering from malignancy
2. Had a high grade fever, coronary obstructive pulmonary disease, or an upper respiratory tract infection
3. Had untreated pneumothorax
4. Had a seizure disorder
5. Were pregnant
6. Required vascular intervention, or who have had vascular surgery in the lower limbs in the last two months
7. Had suspected poor compliance

RESULTS

1. Number Of Patients

As shown in the distribution of patients in groups ***(Figure 1)***, a total of 48 patients underwent HBOT, and 49 were included in the non-HBOT group.

Each patient in the HBOT group underwent 35.41 sessions for a period of 90 minutes at 2.5 ATM.

	HBOT	Non-HBOT
Number of patients	48	49

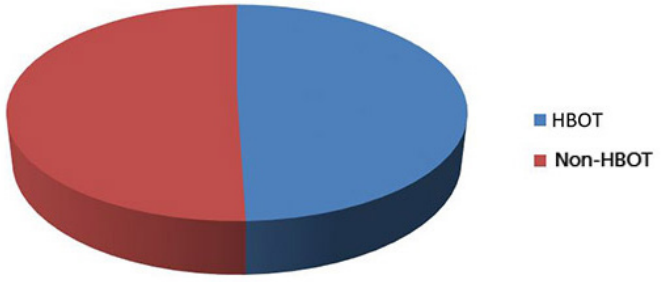

Figure 1. The distribution of patients in groups.

2. Age Distribution

The age range of patients in both groups was between 29-69 years old ***(Figures 2a and 2b).*** The greatest number of patients in both the groups represented those between 46-60 years old. The average age of the HBOT group and non-HBOT group patients was 53.83 and 56.4 years old respectively, with a p-value of 0.165.

Age Groups (Years)	HBOT (48)	Non-HBOT (49)
<30	2	0
30-45	9	7
46-60	19	24
>60	18	18

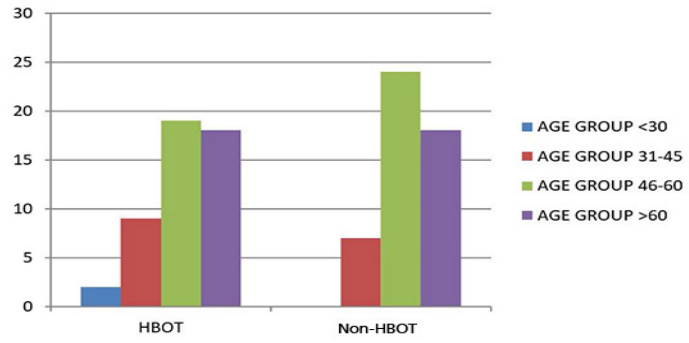

Figure 2a. Age distribution in the study groups.

	HBOT	Non-HBOT	P-value
Average age (years)	53.83	56.4	0.165

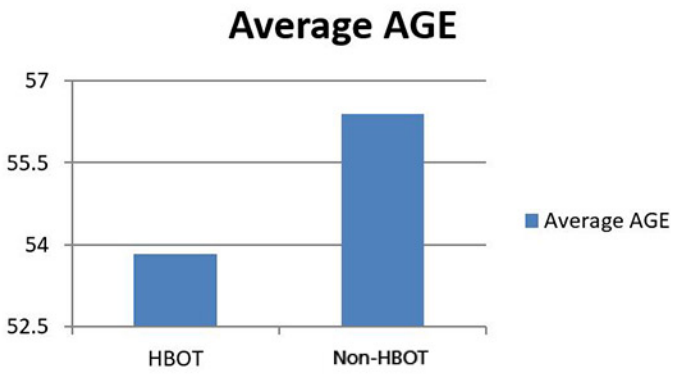

Figure 2b. Graphical depiction of age distribution.

3. Gender Distribution

Males outnumbered the females in both the groups ***(Figure 3);*** 77.08% in the HBOT group and 67.34% in the non-HBOT group were males.

Sex	HBOT (48)	Non-HBOT (49)	P-value
Male	37 (77.08%)	33 (67.34%)	0.289
Female	11 (22.91%)	16 (32.65%)	

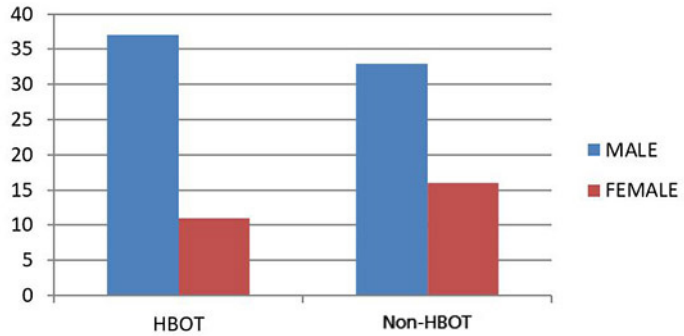

Figure 3. Gender distribution among patients in the study groups.

4. Ulcer Wagner Grade

Patients belonging to Wagner grade 2, 3 and 4 were included in the study. The greatest number of patients in both groups belonged to Wagner grade 4 ***(Figure 4)***.

Wagner Grade	HBOT (48)	Non-HBOT (49)	P-value
2	5 (10.41%)	7 (14.28%)	0.522
3	12 (25%)	13 (26.53%)	
4	31 (64.58%)	29 (59.41%)	

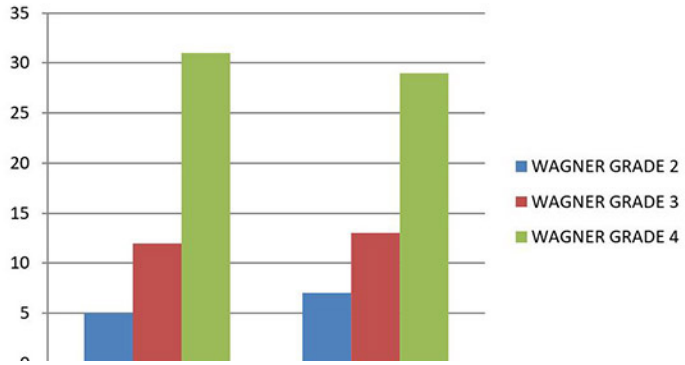

Figure 4. Ulcer distribution among study groups according to Wagner's classification.

5. Duration of Diabetes Mellitus

The duration of diabetes ranged from 1- 28 years in the HBOT group and from 1-26 years in the non-HBOT group ***(Figure 5)***.

	HBOT	Non-HBOT	P-value
Average duration of diabetes mellitus (years)	12	14.59	0.06

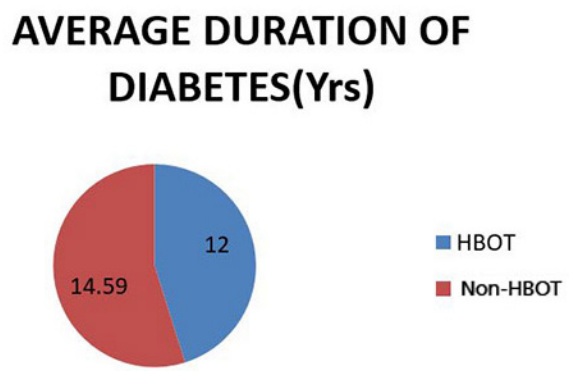

Figure 5. Average duration of diabetes mellitus.

6. Anti-Diabetic Medication

A majority of the patients in both groups were on insulin therapy. ***(Figure 6)***.

Anti-Diabetic Mellitus Medication	HBOT (48)	Non-HBOT (49)	P-value
OHA	21	17	0.366
Insulin	27	32	

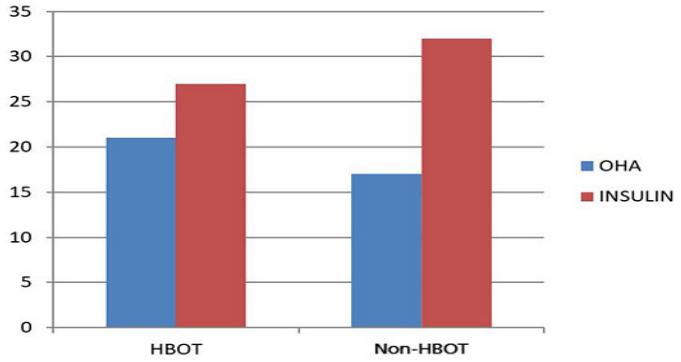

Figure 6. Anti-diabetic mellitus medication distribution among study groups.

7. Ankle-Brachial Index (ABI)

The average ABI in the HBOT group was 0.68 and 0.69 in the non-HBOT group ***(Figure 7)***.

	HBOT	Non-HBOT	P-value
Averge ABI (mm Hg)	0.68	0.69	0.568

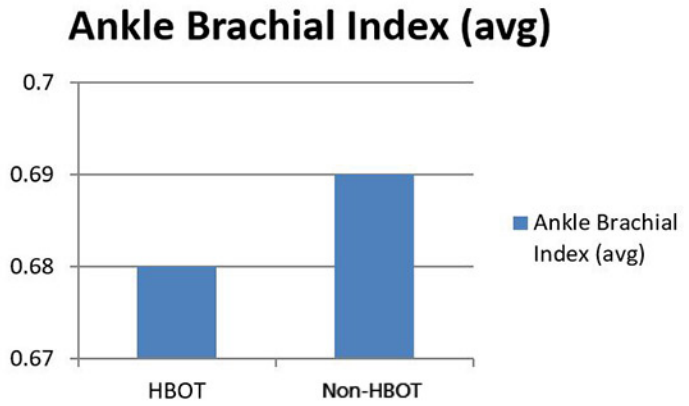

Figure 7. Average ABI among study group participants.

8. HbA1c

The average HbA1c in the HBOT group was 8.3 and 8.9 in the non-HBOT group ***(Figure 8).***

	HBOT	Non-HBOT	P-value
Avg HbA1c (%)	8.3	8.9	0.061

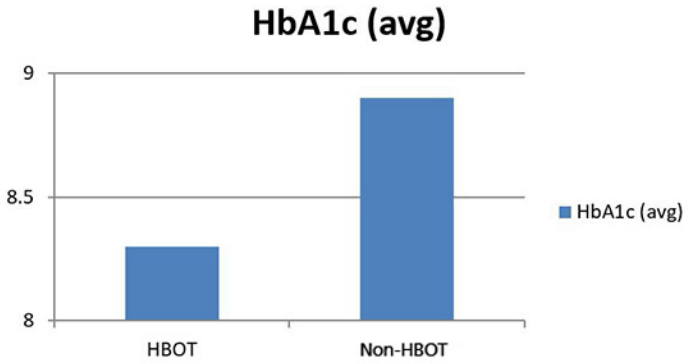

Figure 8. Average HbA1c among study group participants.

9. Risk Factors

There were no statistically significant differences in the HBOT and Non-HBOT groups regarding risk factors such assmoking, hyperlipidemia, obesity, coronary artery disease, prior stroke, proteinuria, renal failure, hypertension, retinopathy, and osteopenia. ***(Figure 9)***

	HBOT (48)	Non-HBOT (49)	P-value
Retinopathy	22	24	0.759
Proteinuria	10	10	0.959
Renal impairment	5	12	0.068
Hypertension	26	29	0.622
Hyperlipidemia	15	12	0.463
Obesity	12	13	0.864
Smoking	16	19	0.58
Coronary artery disease	20	23	0.60
Prior stroke	4	3	0.678
Osteopenia	21	30	0.086

Retinopathy is defined as fundus oculi by ophthalmologist.
Proteinuria is defined as an albumin excretion rate >200 mg/24 h.
Renal impairment is defined as creatinine >1.3 mg/dl.
Hypertension is defined as systolic blood pressure >160 mm Hg and/or diastolic blood pressure >95 mm Hg or on antihypertensive therapy.
Hyperlipidemia is defined by triglyceride 180mg/dl or higher, cholesterol 200mg/dl or higher and low-density lipoprotein 160mg/dl or higher, or on hypolipidemic therapy.
Obesity is defined as a BMI >24 and >25 kg/m2 for women and men, respectively.
Smokers were defined as current active smokers or those who had quit within 2 months of presentation.
CAD is defined by resting electrocardiogram and B mode echocardiography.
Osteopenia was determined by radiographic findings.

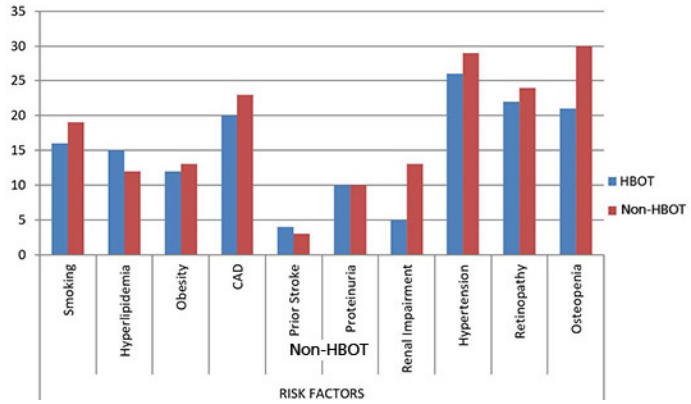

Figure 9. Distribution of risk factors in study group participants.

10. Infection and Recovery

The rate of infection recovery in the HBOT group was 79.06%, whereas it was 47.61% in the non-HBOT group ***(Figure 10)***. The result was found to be statistically significant in correlation between infection recovery, favoring HBOT group ($p<0.05$).

	HBOT (48)	Non-HBOT (49)	P-value
Avg HbA1c (%)	8.3	8.9	0.061

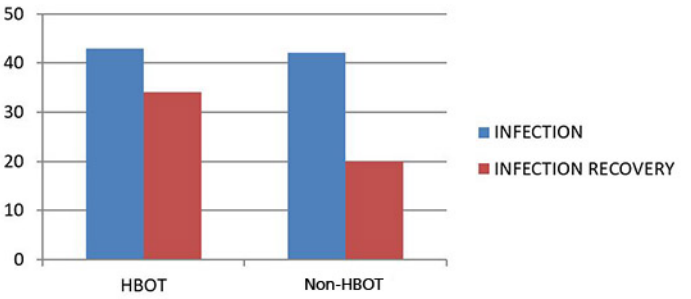

Figure 10. Infection and recovery in the study group participants.

11. Outcomes By Intervention and Grade *(Figure 11)*

Outcome	Ulcer Grade 2 (n=12)		Ulcer Grade 3 (n=25)		Ulcer Grade 4 (n=60)	
	HBOT (n=5)	n-HBOT (n=7)	HBOT (n=12)	n-HBOT (n=13)	HBOT (n=31)	n-HBOT (n=29)
Healed (n=32)	5	0	7	1	19	0
Graft or flap (n=4)	0	0	0	0	3	1
Distal amputation (n=27)	0	2	5	11	4	5
Proximal amputation (n=16)	0	0	0	0	1	15
Debridement (n=9)	0	2	0	1	0	6
No change (n=9)	0	3	0	0	4	2

Healed = complete closure without debridement in the operating room.
Graft or flap = graft or flap closure required.
Distal amputation = amputation distal to metatarsophalyngeal joints.
Proximal amputation = amputation proximal to metatarsophalyngeal joints.
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.

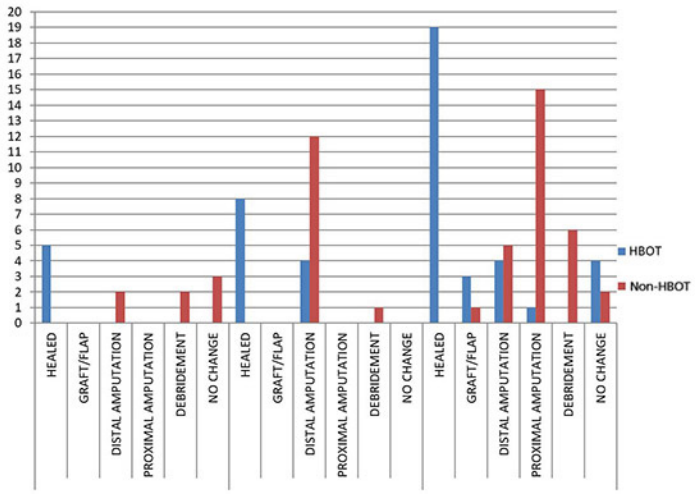

Figure 11. Outcomes on the basis of intervention and grade in the study group participants.

12. Healing Rate

Healing rate was defined as complete epithelial closure of the wound without debridement or any operative procedure in the operating room. Healing rate in the HBOT group was 64.58% and 2% in the non-HBOT group ***(Figure 12)***. The result was found to be statistically significant in correlation between healing rates, favoring HBOT group ($p<0.05$).

	HBOT (48)	Non-HBOT (49)	P-value
Healing rate	31 (64.58%)	1 (2%)	0.000000000001

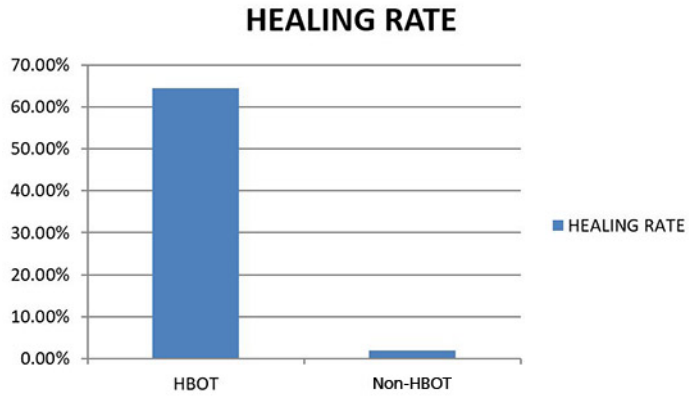

Figure 12. Comparison of healing rates between study group participants.

13. Number of Amputations (Proximal + Dorsal)

In the HBOT group 10 out of 48 patients underwent an amputation, while in the non-HBOT group 31 out of 49 patients underwent an amputation ***(Figure 13).***

The result was found to be statistically significant in correlation between number of amputations, favoring the HBOT group ($p<0.05$).

Amputations	HBOT (48)	Non-HBOT (49)	P-value
Proximal	1	15	
Distal	9	18	
Total	10 (20.83%)	31(63.26%)	0.00000001

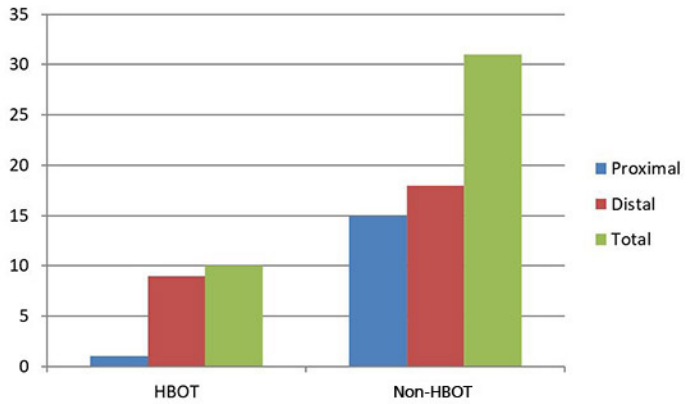

Figure 13. Types and total amputations.

14. Number of Operative Procedures

Operative procedures included amputations, graft/flap closure, and debridement in the operating room.

Thirteen out of 48 patients in the HBOT group underwent operative procedures, and 43 out of 49 patients in the non-HBOT group underwent operative procedures, making the result statistically significant ($p<0.05$), favoring HBOT group ***(Figure 14).***

Operative Procedure	HBOT (48)	Non-HBOT (49)	P-value
Graft/flap closure	3	1	
Proximal amputation	9	18	
Distal amputation	1	15	
Debridement	0	9	
Total	13 (27%)	43 (87.75%)	0.00000000001

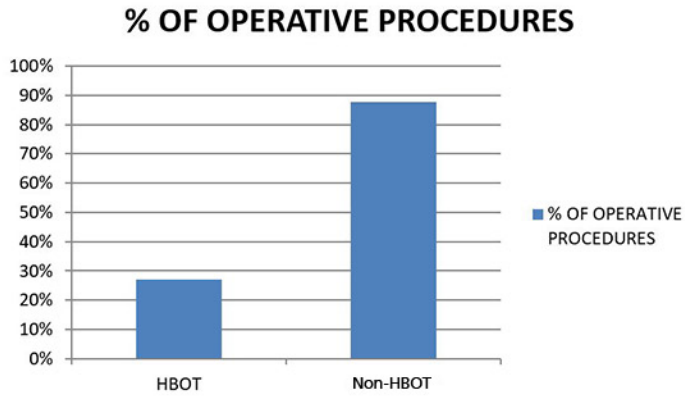

Figure 14. Comparison between operative procedures in both study groups.

15. Length of Hospital Stay

The average hospital length of stay among participants in the HBOT group was 30.68 days and 52.4 days for participants in the non-HBOT group ***(Figure 15)***.

The result was found to be statistically significant in correlation between hospital length of stay, favoring HBOT group ($p<0.05$).

	HBOT	Non-HBOT	P-value
Avg HbA1c (%)	8.3	8.9	0.061

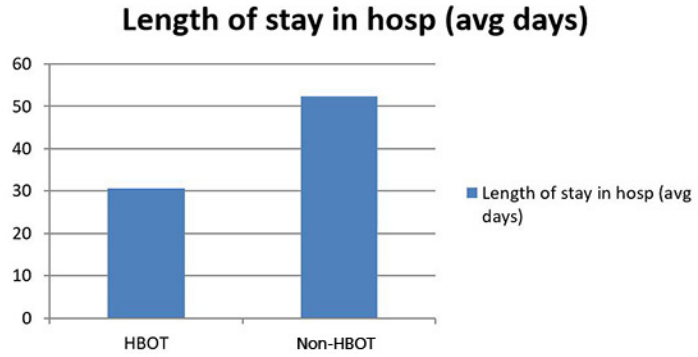

Figure 15. Average length of hospital stay among study group participants.

ANALYSIS

This was a prospective study conducted in the Department of General Surgery in a tertiary referral hospital, and was performed between July 2013 and October 2015 to evaluate the role of HBOT in chronic non-healing diabetic foot ulcers. Patients in the study group were given HBOT, while those in the control group were not given HBOT. Ninety seven patients participated in the study; 48 belonged to the HBOT group and 49 to the non-HBOT group. The patients in both the groups were between 29–69 years old. The mean age of HBOT group and non-HBOT participants was 53.83 and 56.4 years old respectively. In both the groups, males outnumbered the females - 77.08% in the HBOT group and 67.34% in the non-HBOT group.

On admission, patients' ulcers were classified according to Wagner's classification, and patients belonging to Wagner's grade 2, 3 and 4 were included in the study. The greatest number of patients in both groups belonged to Wagner's

grade 4 (ie, 64.58% in HBOT group and 59.41% in non-HBOT group). Patients were evaluated on the presence of risk factors like HbA1c levels, ABI, duration of diabetes mellitus, type of anti-diabetic medication, presence of retinopathy, proteinuria, renal impairment, hypertension, hyperlipidemia, obesity, smoking, coronary artery disease, prior stroke, osteopenia, and presence of infection. There were no statistically significant differences in the HBOT and non-HBOT groups with regards to these risk factors.

The rate of infection recovery in the HBOT group was 79.06% (34 out of 43), whereas in the non-HBOT group, it was 47.61% (20 out of 42). The result was found to be statistically significant, favoring HBOT group. The healing rate in participants in the HBOT group was 64.58% (31 out of 48) and 2% (1 out of 49) in the non-HBOT group. The result was found to be statistically significant, favoring HBOT group. In the HBOT group, 20.83% (10 out of 48) patients underwent amputation, while in the non-HBOT group 63.26% (31 out of 49) underwent amputation. The result was statistically significant, favoring HBOT group. Amputations included both proximal and distal. Twenty-seven percent of patients (13 out of 48) in the HBOT group underwent operative procedures, whereas 87.75% patients (43 out of 49) in the non-HBOT group underwent operations. The difference was statistically significant. Operative procedures included amputations, graft/flap closure, and debridement in the operating room. The hospital average length of stay among participants in the HBOT group was 30.68 days and 52.4 days for participants in the non-HBOT group. The result was statistically significant, favoring the HBOT group.

CONCLUSION

HBOT offers a significant advantage over the traditional method of treatment of diabetic foot ulcers. The overall rate of recovery from infection is definitely higher among patients receiving HBOT. Patients undergoing HBOT have a higher rate of healing as compared to those being subjected to standard therapy. Patients subjected to HBOT treatment have a lesser chance of undergoing amputation. HBOT helps in reducing the total number of costly operative procedures that a patient may be subjected to, which include amputations, graft/flap closures, and debridement. It indirectly has an effect on the patient's hospital expenses. The hospital length of stay is reduced in patients undergoing HBOT, thus reducing the inconvenience and expenses allowing effective utilization of hospital resources. HBOT enhances the healing of ischemic, non-healing diabetic leg ulcers and may be used as a valuable adjunct to conventional therapy when reconstructive surgery is not possible. There is a reason for continuing the use of HBOT for diabetic foot ulcers as an adjunct to the standard therapy. It offers advantages in treatment of chronic non-healing diabetic foot ulcers, and the technique should be offered on a wider basis. The cost of the HBOT will be reduced as it becomes more widely available in clinical settings, and as further knowledge of its other advantages, such as limited side effects and relative safety, become more widely appreciated.

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