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RESEARCH ARTICLE

HEALING EFFECT OF HYPERBARIC OXYGEN THERAPY AS AN ADJUNCTIVE TREATMENT ON DIABETIC FOOT ULCER PATIENTS IN SHORT DURATION- A BRIEF REPORT

[1]Ezhilarasi Krishnamoorthy, [2]Abirami Palani and [2,*]Vijay Viswanathan

-Department of Biochemistry and Molecular Genetics, Prof. M. Viswanathan Diabetes Research Centre and M.V. Hospital for Diabetes (WHO Collaborating Centre for Research, Education and Training in Diabetes), No. 4, West Madha Church Road, Royapuram, Chennai 600013, Tamil Nadu. India

[2]Department of Podiatry, Prof. M. Viswanathan Diabetes Research Centre and M.V. Hospital for Diabetes (WHO Collaborating Centre for Research, Education and Training in Diabetes), No. 4, West Madha Church Road, Royapuram, Chennai 600013, Tamil Nadu. India

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ABSTRACT

Aims/purpose: The aim of the study was to determine the healing effect of HBOT as an adjunctive treatment on Diabetic foot ulcer patients (DFU) in short duration compared to the standard wound therapy (ST).

Methodology of study: The study was conducted among 6 consecutively attending patients with diabetic foot ulcers (DFU) and with grade III or IV Wagner classification of foot ulcers were recruited in the podiatry clinic. Patients randomized to the control group (n = 3) received standard care including offloading, wound debridement, and glucose control. HBOT group patients (n = 3) received standard care and daily HBOT sessions for 90 minutes at 2.5 atmospheres absolute (ATA) for 2 weeks. Ulcer tissues were harvested on days 0, 7 and 14 to determine the histological changes between HBOT and non HBOT groups. The anthropometric and biochemical values are recorded in the baseline level.

Findings: There was no statistical difference noticed between baseline characteristics of two groups. The histological examinations of the ulcer at the baseline were found to have inflammation with edema in both the group. On 7th day fibres were associated with thickened vessel, no vasculitis in the HBOT treated patients and acute ulcer with inflammatory cells was noted in the standard treatment patients. At the end of the treatment granulation tissues with proliferating capillaries were seen more in the HBOT treated patients. In ST group, acute ulcer with fibrin exudates was noted

Conclusion and Implications: In conclusion, it can be stated that HBOT therapy has a positive effect in initiating the healing process of ulcer than standard treatment. We believe that HBOT is a useful adjunct in the treatment of diabetic foot ulcers, and that the cost of HBOT itself will be reduced as it becomes more widely available in the clinical settings..

INTRODUCTION

Diabetic foot ulcer (DFU) affects approximately 10–15% of the diabetic population (Chiwanga *et al,* 2015). In India, the prevalence of DFU in the clinic population is 3.6% (Pendsey, 1994) and it was found that patients without foot problems spent 9.3% of the total income, while patients with foot problem had to spend 32.3% of the total income towards treatment (Shobhana *et al,* 2000). Non healing ulcer is a highly morbid condition requiring hospitalization as long as 2-6 weeks for full recovery despite a multidisciplinary approach associating glycemic control daily local care, foot offloading, antibiotic therapy, and surgical revascularization which are considered to be a standard therapy (ST) for lower extremity wounds (Bentkover *et al,* 1993, Thomas, 1999). Another current option for the treatment of DFU is hyperbaric oxygen therapy (HBOT). It involves inhalation of 100% oxygen inside a pressurized hyperbaric chamber and has been used successfully in humans at varying pressures to treat a range of conditions (Sheffield *et al,* 2002). HBOT treatment showed improved healing rate of DFU in short term but not in long term and it was well recognized that the change in wound size at 2 weeks and 4 weeks is a predictor of complete healing after 12 weeks (Sheehan *et al,* 2006, Kranke *et al,* 2012). Study showed that prolonged treatment of HBOT should be avoided as it increases oxidative stresses which are considered as an important pathogenesis of chronic non healing wounds (Schafer *et al,* 2008, Le *et al,* 2013). Only limited number of studies is available regarding the short term administration of HBOT to DFU patients.

Corresponding author: **Vijay Viswanathan,**
Department of Podiatry, Prof. M. Viswanathan Diabetes Research Centre and M.V. Hospital for Diabetes (WHO Collaborating Centre for Research, Education and Training in Diabetes), No. 4, West Madha Church Road, Royapuram, Chennai 600013, Tamil Nadu. India.

The objective of the study was to determine the healing effect of HBOT as an adjunctive treatment on DFU patients in short duration compared to the standard wound therapy.

MATERIALS AND METHODS

The T2DM patients attending the podiatric clinic at tertiary care centre diagnosed with DFU with Wagner wound grade 3 or 4 was eligible to participate in the study.

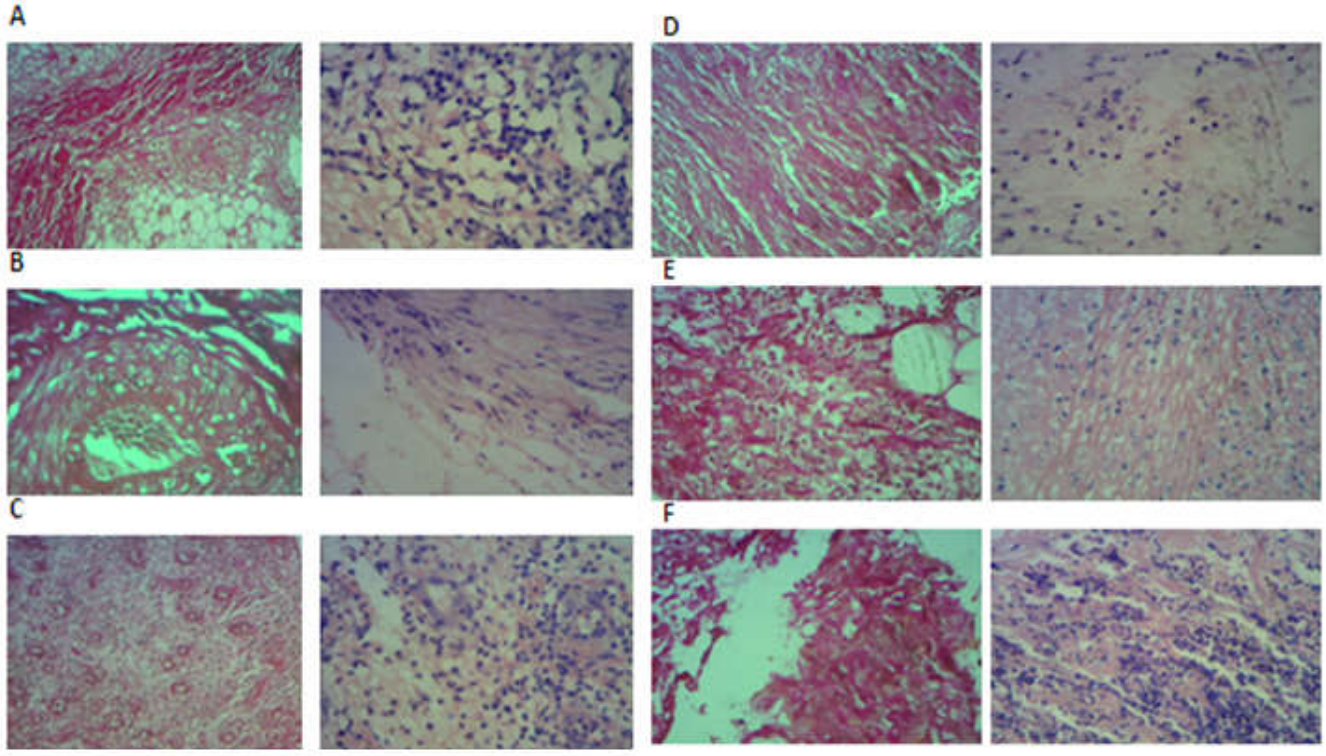

Fig. 1. Haematoxylin and eosin stained and Van-Gieson stained wound tissue sections taken on (A) Baseline, (B) 7th day (C) 14th day of HBOT treatment, (D) Baseline, (E) 7th day and (F) 14th day of normal intervention

A total of 6 DFU patients were recruited and followed up on 7th and 14th day of the treatment. Among 6 patients, 3 were given 90 minutes of HBOT for 14 days along with standard wound treatments and 3 were given standard wound treatment alone. Standard wound therapy is defined as an aggressive local debridement, vascular assessment, tight blood glucose control, optimization of nutritional status, resolution of infection with antibiotic therapy, off-loading the joint and maintenance of a clean and moist wound bed. The samples were collected from the patients. Anthropometric measurements and biochemical parameters were recorded. Histopathological examination was performed using Haematoxylin-Eosin (HE) and van Gieson staining. The following parameters were used for histological description: 1) presence and severity of hyperkeratosis; 2) presence and severity of fibrosis; 3) number and integrity of cutaneous annexes and capillaries; 5) presence and distribution of inflammatory reaction, cellular, bacterial debris and granulating tissue. All of these items were evaluated and the results were expressed as absent (no presence of any of the considered parameter), scarcely present (parameter detected on < 33% of the lesions' preparations), present (parameter found in 33– 66% of preparations), and intensively present (parameter found in >66% of preparations) (Alberto *et al,* 2003). The data was entered and analyzed using SPSS statistical package (Version 12.0; SPSS, Chicago, IL). Chi square test was applied to analyze categorical variable and P value less than 0.05 was considered significant.

RESULTS

Table 1 shows the baseline characteristics of biochemical and anthropometric parameters among HBOT and ST patients. There was no statistical difference noticed between baseline characteristics of two groups.

Figure 1 shows the histological examinations of the study patients. At the baseline the ulcer was found to have inflammation with edema in both the group. On 7th day fibres were associated with thickened vessel, no vasculitis in the HBOT treated patients and acute ulcer with inflammatory cells was noted in the standard treatment patients. At the end of the treatment granulation tissues with proliferating capillaries were seen more in the HBOT treated patients. In ST group, acute ulcer with fibrin exudates was noted.

HBOT treatment

A. Collagenized septa, adipose tissue, capillaries and inflammation (0 day).
B. Thickened vessel wall with fibrous media. No vasculitis and subcutaneous fat (7th day).
C. Granulation tissue with proliferating capillaries (14th day).

Standard treatment

D. Bright eosinophilic collagen fibres seen. Acute inflammation with edema noted (0 day).
E. Acute ulcer with inflammatory cells noted. Acute ulcer and the fibrin exudates were seen (7th day).
F. Bright eosinophilic collagen fibres with tiny yellow collagen seen. Acute ulcer with fibrin exudates was seen (7th day).

Table 1. Anthropometric and biochemical parameters of HBOT and non-HBOT subjects at baseline (n=6)

Parameters	HBOT(n=3)	Non-HBOT(n=3)	p-value
Age(Yrs)	55.6±15.3	61 ± 13.5	0.67
BMI(Kg/ m^2)	29.6±10.7	22.9±3.4	0.36
Diabetic Duration(Yrs)	13±8.1	10±7.2	0.65
Systolic (mmHg)	126.6±5.7	123.3±15.2	0.74
Diastolic(mmHg)	76.6±5.7	80±10	0.63
Fasting glucose(mg/dl) 2 hr	235±159.4	160.6±77.7	0.5
Post prandial (mg/dl)	241.3±155.9	275.3±136.5	0.79
Urea(mg/dl)	49.3±43.3	56±20.8	0.82
Creatinine (mg/dl)	1.2±0.5	1.5±0.5	0.5
HbA1c	9.6±1.2	9.9±2.2	0.84
Haemoglobin(g/dl)	11.2±2	10.7±0.6	0.7
Triglyceride(mg/dl)	137±31.1	112±33.1	0.39
Total Cholesterol (mg/dl)	153±32.5	176.3±93.6	0.7
HDL (mg/dl)	26.5±2.12	36.3±12.7	0.25
LDL(mg/dl)	96±33.9	100.6±65.3	0.91
VLDL(mg/dl)	30.5±3.5	39.3±16.5	0.41
Uric acid(mg/dl)	4.0±1.3	5.9±1.3	0.14
Neuropathy*	3/3	3/3	
Insulin + OHA*	3/3	3/3	
Ulcer locations Heel* (%)	1 (33.3)	1 (33.3)	
Toe (%)	2 (66.7)	0(0)	0.603
Dorsal (%)	0 (0)	2 (66.7)	
Wagner classification*			
Grade III	1/3(33.3)	1/3(33.3)	1
Grade IV	2/3(66.7)	2/3(66.7)	
Days of hospital admission	15.3±10.1	20.3± 13.5	0.63

*Results are expressed as mean ± SD unless specified. OHA – Oral hypoglycemic agent

DISCUSSION

This prospective study provides evidence that HBOT fasten the healing rate of DFU. In addition, it suggests the possibility of shortening hospitalization time. After 14 days of the treatment, the patients on HBOT treatment achieved a favorable healing rate which was evident from histopathological features. It is generally understood that tissue hypoxia is a significant factor in the etiology of nonhealing foot ulcers in diabetic patients and HBOT through its correct action on peripheral ischemia helps in promoting healing (Fife *et al,* 2002). HBOT enhances healing by increasing oxygen gradient which promotes the formation of new vessels required for wound healing, and increases fibroblast proliferation and collagen production (Wattel *et al,* 2005, Kessler *et al,* 2003). HBOT also reduces inflammation promoting angiogenesis, fibroblast function, and granulation by reducing the expression of pro inflammatory cytokines (Thackham *et al,* 2008, Londahl *et al,* 2013, Tiaka *et al,* 2012).

In particular, a difference was apparent for granulation tissue, fibrosis, reduction inflammation, cellular debris and formation of capillaries in HBOT treated patients compared to the patients receiving standard therapy. The other parameters like hyperkeratosis and adnexa were found to have no difference. The positive contribution to granulation and capillaries formation following HBOT therapy shows the acceleration effect of HBOT on histological healing. The limitation of this study is that due to the pilot nature of the study, sample size was limited. Another limitation is that the time taken for complete healing of the DFU was not studied. This study could have been enhanced by simultaneously measuring markers of oxidative stress and correlating with healing process. In conclusion, the HBOT has a positive effect in initiating the healing process of ulcer than standard treatment. It may also be cost-effective when measured against outcomes such as amputations, repeated debridement, hospital stay and psychological disability. HBOT is a useful adjunct in the treatment of DFU, and that the cost of HBOT itself will be reduced as it becomes more widely available in the clinical settings.

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Contribution

EK wrote, contributed to discussion and edited the manuscript. AP collected the samples and performed the experiment. VV conceived the concept, contributed to discussion and reviewed the manuscript.

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REFERENCES

Alberto, P., Paolo, V., Loredana, R., Giuseppe, N., Fabio, B., Marco, R., Virna, Z., and Stefano Del, P. 2003. Semiquantitative Analysis of the Histopathological Features of the Neuropathic Foot Ulcer. *Diabetes Care*, 26(3) bc, 123–3128.

Bentkover, J. D., and Champion, A. H. 1993. Economic evaluation of alternative methods of treatment for diabetic

foot ulcer patients: cost effectiveness of platelet release and wound care clinics. *Wound,* 5, 207-215.

Chiwanga, F.S., and Njelekela, M. A. 2015. Diabetic foot: prevalence, knowledge, and foot self-care practices among diabetic patients in Dar es Salaam, Tanzania – a cross-sectional study. *J Foot Ankle Res*, 8, 1-7.

Fife, C.E., Buyukcakir, C., Otto, G. H., Sheffield, P. J., Warriner, R. A., Love, T. L., and Mader, J. 2002. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients. *Wound Repair Regen*, 10(4), 198-207.

Kessler, L., Bilbault, P., Ortega, F., Grasso, C., Passemard, R., Stephan, D., Pinget, M., and Schneider, F. 2003. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care*, 26(8), 2378-82.

Kranke, P., Bennett, M. H., Martyn-St James, M., Schnabel, A., and Debus, S. E. (2012). Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*, 4, 41-23.

Le Ma, M. D., Pingsong Li, M. D., Zehong Shi, M. D., Tuanjie Hou, M. D., Xiao Chen, M. D., and Jin Du, M. D. 2013. A Prospective, Randomized, Controlled Study of Hyperbaric Oxygen Therapy: Effects on Healing and Oxidative Stress of Ulcer Tissue in Patients with a Diabetic Foot Ulcer. *Ostomy Wound Manage*, 59(3), 18-24.

Londahl, M. 2013. Hyperbaric oxygen therapy as adjunctive treatment of diabetic foot ulcers. *Int J Low Extrem Wounds*, 12,152-157.

Pendsey, S.P. 1994. Epidemiological aspects of diabetic foot. *Int J Diab Dev Countries,* 14, 37-38.

Schafer, M., and Werner, S. 2008. Oxidative stress in normal and impaired wound repair. *Pharmacol Res*, 58(2), 165-171.

Sheehan, P., Jones, P., Giurini, J.M., Caselli, A., and Veves, A. 2006. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Plast Reconstr Surg*, 117(7), 239-244.

Sheffield, P.J., and Smith, P.S. 2002. Physiological and pharmacological basis of hyperbaric oxygen therapy. In: Bakker DJ, Cramer FS (eds). *Hyperbaric Surgery Perioperative Care*, 63-110.

Shobhana, R., Rama Rao, P., Lavanya, A., Vijay, V., and Ramachandran, A. 2000. Cost burden to Diabetic patients with foot complications- a study from Southern India. *JAPI*, 48(12), 1147-1150.

Thackham, J.A., McElwain, D.L., and Long, R.J. 2008. The use of hyperbaric oxygen therapy to treat chronic wounds: a review. *Wound Repair Regen*, 16, 321-330.

Thomas, P.K. 1999. Diabetic peripheral neuropathies: their cost to patient and society and the value of knowledge of risk factors for development of interventions. *Eur Neurol*, 41, 35-43.

Tiaka, E.K., Papanas, N., Manolakis, A.C., and Maltezos, E. 2012. The role of hyperbaric oxygen in the treatment of diabetic foot ulcers. *Angiology*, 63, 302-314.

Wattel, F., and Mathieu, D. 2005. Oxygen and wound healing. *Bull Acad Natl Med*, 189(5), 853-64.

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