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Role of Hyperbaric Oxygen Therapy in Diabetic Foot Wounds: A Prospective Observational Study in a Tertiary Care Centre

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Abstract
Diabetic foot ulcer represents a major health problem globally. Hyperbaric oxygen therapy (HBOT) has been recommended and used in wound ulcers. Hence the present study was undertaken to evaluate whether hyperbaric oxygen can decrease major amputation rates and achieve wound healing in chronic non-healing wounds. A total of 112 patients were treated with HBOT as an adjunct to standard treatment modality for their diabetic foot ulcer. Outcome was assessed in terms of ulcer healed, ulcer requiring further debridement and non-healing ulcer leading to higher level amputation. Of 112 patients, 73 were completely healed, 19 needed further debridement and 23 underwent amputation. Of the amputations, 9 were below knee amputation, 5 were above knee amputation and 9 were minor. Major amputations were associated with the Wagner grade 4, with the age of the patients and with the age of the wounds (>10 weeks). Although there is some indication of a beneficial effect on wound healing, it is currently unknown which patients are likely to benefit from HBOT and which patients are not. If patient is clinically fit to undergo HBOT, then HBOT can be considered as an adjunct to standard care in all chronic non-healing wounds. TcPO2 as the only objective criteria for determining efficacy of HBOT does not hold true in all patients. TcPO2 <40 mm Hg after completion of HBOT can predict poor outcome.

INTRODUCTION

Diabetic foot ulcer is a pathological condition that arises from diabetes and represents a major health problem throughout the world[1]. It is estimated that about 15-25% of patients with diabetes may develop foot ulcers during their lifetime[2]. These wounds are often resistant to healing; therefore, people with diabetes experience lower limb amputation at about 20 times the rate of people without diabetes[3]. If an ulcer does not heal with standard wound care, other therapeutic interventions are offered, one of which is hyperbaric oxygen therapy (HBOT).

HBOT for diabetic ulcers involves intermittent administration of 100% oxygen, usually in daily sessions of 90 minutes each, at pressures of 1.5 atmospheres absolute (ATA) in an airtight cabin[4,5]. By increasing the blood oxygen content, HBOT creates a favourable gradient for the diffusion of oxygen into the tissues. In hypoxic tissues, the enhanced oxygen supply has multiple effects that may benefit wound healing. By increasing the expression of, among others, vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), HBOT may enhance angiogenesis and fibroblast proliferation. In addition, the resulting hyperoxia may cause vasoconstriction, thereby decreasing tissue oedema. By reducing the expression of pro-inflammatory cytokines, HBOT reduces inflammation, while simultaneously enhancing the bacterial killing activity of leukocytes[5,6].

Although pooled estimates from randomized clinical trials (RCTs) on HBOT in patients with diabetic ulcers in early systematic reviews demonstrated increased rates of wound healing and decreased major amputation rates when HBOT was added to standard care[7], the reduction in amputation rates was not confirmed in a recent large trial[8]. The subsequently updated Cochrane review reported increased rates of ulcer healing in the short term (risk ratio (RR) 5.20, 95% CI: 1.25-21.66) but not in the long term (RR 9.53, 95% CI: 0.44-207.76) and no significant difference in major amputation rates (RR 0.36, 95% CI: 0.11-1.18)[9]. These results were confirmed in the meta-analysis by O' Reilly[10]. Given that the findings of an additional RCT were recently reported, a systematic review of all currently available RCTs has been performed to assess whether HBOT, when added to current best practice, can effectively improve wound healing and prevent amputations in patients with diabetic foot ulcers.

MATERIALS AND METHODS

SA total of 112 diabetic patients with chronic non-healing ulcer in their feet were presented to tertiary care centre during the period from June 2015 -Dec 2018 were included in this study. On admission, diabetic foot wounds were classified according to Wagner classification system. Diabetes mellitus type, duration of diabetes, type of diabetes treatment, age of diabetic wound, previous diabetic ulcer history, diabetic foot deformity and smoking habits were recorded. Glycosylated haemoglobin levels were measured. Consultations were obtained so as to determine neuropathy, nephropathy, retinopathy and arterial disease requiring surgical/vascular intervention. Outcome was assessed in terms of ulcer healed, ulcer requiring further debridement and non-healing ulcer leading to higher level amputation. Patients were followed up till complete healing of primary ulcer, healing of wound requiring further debridement after completion of HBOT sessions and healing of amputation stump in patients landed up in higher level amputation after completion of HBOT sessions.

Definition of Chronic Non-Healing Ulcer: Chronic non-healing ulcer was defined as ulcer not healing after standard wound care has been provided for at least 4 weeks.

Standard Wound Care: It included radical debridement, dressing change at regular intervals, vascular screening for significant peripheral arterial disease and or local tissue hypoxia, adequate off loading, proper antibiotic therapy which means culture sensitive antibiotic after obtaining deep tissue culture and giving antibiotic through intravenous injection for minimum period of 12 days or putting antibiotic beads within wound bed complemented with oral antibiotic and use of negative pressure wound therapy wherever required.

Ischemic Ulcer: Patients with significant peripheral vascular disease (PVD) (N=81) underwent peripheral angiography and angioplasty (N=55) or bypass procedure (N=6). 20 patients with PVD were not suitable candidates for any kind of peripheral vascular intervention because of following reasons: significant below popliteal triple vessel disease, long segment stenosis/occlusion in above knee vessel with poor distal run off, poor cardiac reserve (EF<30%), patient not willing to take risk of peripheral angioplasty or bypass procedure.

Vasculitis: Patients without significant PVD with chronic non healing ulcer over atypical sites over foot like dorsum of foot, lower one third of leg medial or lateral side, multiple ulcers over leg with severe pain at ulcer site were biopsied in outpatient department. Histopathological examination of these ulcers revealed leukocytoclastic vasculitis (n=16) which was treated with intravenous Cyclophosphamide therapy with oral steroids as advised by rheumatologist.

Venous Ulcer: Patients with relatively young or middle age presenting with not-painful ulcer over medial or lateral malleolus or along the path of perforators, assessed by venous Doppler found to have venous ulcer (n=5). These patients were first managed conservatively for cellulitis associated with ulcer followed by endovenous procedure for varicose veins or incompetent perforators followed by compression dressing with HBOT.

Necrotizing Fasciitis: Patients with necrotizing fasciitis (N=6) underwent radical debridement, antibiotics according to culture sensitivity report, good glycemic control with HBOT.

Burn Injury: Patients with burn injury (N=4) over feet were managed with intravenous antibiotics, strict off-loading and HBOT.

Administration of Hyperbaric Oxygen Therapy: Patient was assessed clinically by in house hyperbaric therapy specialist physician for fitness to undergo HBOT.

Criteria for inclusion included: 1) Ejection fraction >40%, 2) Absence of acute systemic illness, acute lower respiratory tract infection, acute middle ear infection, 3) Hemodynamic stability and 4) Absence of claustrophobia.

Criteria for exclusion included: 1) Ejection fraction <40%, 2) Presence of acute febrile illness, 3) Loss of follow up of patient, death of patient from comorbidities, 4) Claustrophobia for chamber, 5) Hemodynamic instability and 6) Wagner wound grade 0, 1, 5.

HBOT was given in monoplace chamber, starting at 1.4 Atmospheric absolute (ATA). After placing the patient in chamber, pressure inside chamber was slowly increased to 1.4 ATA within a period of 15 mins, followed by 60 minutes duration of therapy and decompression in last 15 minutes so each session lasted 90 minutes. Initially patients started with 1.4 ATA and pressure slowly increased to highest level of 2.2 ATA once patient was fully acclamatised over a period of 2-3 days. Therapy was given over 6 days a week, total such 15 sessions followed by a gap of 7 days before the next cycle of HBOT sessions. The uppermost limit of pressure was adjusted taking into consideration the patient's cardiac and pulmonary function, comfort level inside chamber. The patient was monitored by a trained nurse during therapy for vital parameters, blood sugar levels.

Role of Transcutaneous Oximetry (TcPO2): Change in transcutaneous oxygen pressure before and after start of HBOT was recorded in all patients. TcPO2 was measured on dorsal and plantar surface of foot just proximal to site of wound or proximal and distal to wound for wound over heel and lower leg. Patients with TcPO2 <40 mm Hg before the start of HBOT showed mixed response to HBOT sessions. Patients with TcPO2 >40 mm Hg before start of HBOT showed good response to HBOT.

Assessment of Ulcer and Patient After HBOT: Each wound was assessed with respect to change in size of wound, depth of wound, change in ulcer bed tissue, TcPO2 near wound and clinical condition of patient. Patients showing generalized improvement in health were continued with further treatment. Patients showing signs of systemic illness like loss of appetite, fever, increase in serum creatinine, leucocytosis were taken up for operative intervention in the form of further debridement or higher-level amputation.

RESULTS AND DISCUSSIONS

A total of 112 patients with chronic non-healing wounds were included in the study. The distribution of ulcer according to Wagner classification was grade 2(n=31), grade 3(n=51), grade 4(n=30). Ulcer healing in different Wagner grades is shown in (Table 1).

Total HBOT sessions were 15-30 for 84 patients. Each session lasted for 90 minutes. 28 patients were given >30 sessions. These included 23 patients with severe PVD with critical limb ischemia (ultimately landed in higher level amputation), 3 patients with necrotizing fasciitis and 2 patients with burn injuries. 81 patients had significant PVD as shown in (Fig. 1).

55 patients underwent peripheral angioplasty, 6 patients underwent femoro-popliteal bypass procedure. 20 patients with significant PVD did not undergo any kind of vascular intervention. Out of 55 patients undergoing peripheral angioplasty, 7 patients required further debridement and 7 patients underwent higher level amputation (14%) (Table 2).

Out of 6 patients undergoing peripheral bypass procedure only 1 patient needed further debridement. Out of 20 patients with severe PVD not feasible for vascular intervention, only 4 patients had healed ulcers, 3 patients required further debridement and 16 patients ultimately required higher level amputation (including 3 patients who needed further debridement) (Table 2).

31 patients without significant PVD had Venous ulcer (n= 5), Leukocytoclastic vasculitis (n=16), Burn injuries (n=4), Necrotizing fasciitis (n=6) (Fig. 1). Ulcers healed in 23 patients and 8 patients needed further debridement (Table 3).

Out of 112 patients in study, 74 patients showed improved TcPO2 (> 40 mm Hg) after HBOT sessions, 28 patients showed persistent low TcPO2 (<40 mm Hg) after HBOT sessions (Table 4). Out of 74 patients with

TcPO2 >40 mm Hg, 7 patients required higher level amputation. Out of 28 patients with TcPO2 <40 mm Hg, 16 patients required higher level amputation (Table 5). TcPO2 was not measured in necrotizing fasciitis and burn wound patients for obvious reasons (n=10).

In the present study, the following group of patients who were medically fit for HBOT were considered for HBOT.

- Diabetic foot wounds Wagner grade 2,3,4 not showing expected healing after standard wound care.
- Diabetic foot wounds with significant PVD, where outcome of peripheral angioplasty or bypass procedure was less than satisfactory.
- Diabetic foot wounds with good outcome of peripheral angioplasty or bypass procedure but wound showing slow response to standard wound care of 4 weeks.
- Diabetic foot wounds with significant PVD where any kind of vascular intervention was not possible.
- Diabetic foot wound with Wagner grade 4 with critical limb ischemia
- Diabetic foot wounds with ischemic plantar or dorsal flap.
- Diabetic foot wounds with associated vasculitis and PVD.
- Diabetic foot wounds because of burn injury with partial gangrene of toes.
- Diabetic patient with chronic non healing wound of sternum.

In our centre, the in-chamber TcPO2 facility is not available. We measured TcPO2 with patient breathing room air. As per recommendation in-chamber TcPO2 >200 mmHg with patient breathing 100% O2 inside the hyperbaric chamber is the single best discriminator between success and failure with HBOT[11]. For our study, we have modified it. We have measured TcPO2 before start of HBOT in all the patients and serially followed it after completion of HBOT sessions. We have correlated TcPO2 readings with clinical improvement in wound healing and as shown in table 4, only 6 patients (with TcPO2 >40 mm Hg after completion of HBOT) out of 89 required higher level amputation while 17 patients out of 23 (with TcPO2 <40 mm Hg after completion of HBOT) landed up with higher level amputation. So, we can observe that TcPO2 <40 mm Hg after completion of HBOT can

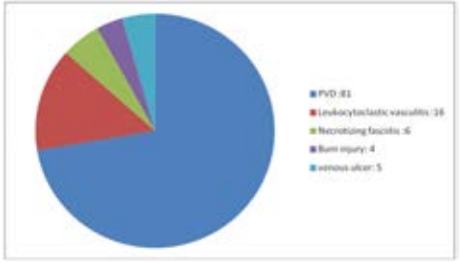


Fig. 1: Distribution of pathological entities in chronic non-healing ulcer in diabetic foot wound

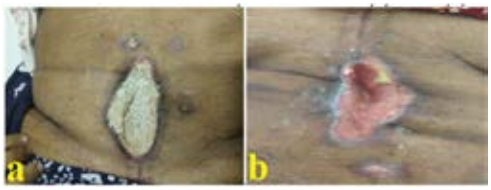
Case 1: a) pre-HBOT, b) post-HBOT

Case 2: Burn injury: a) pre-HBOT, b) post-HBOT

Case 3: Ischemic toe with severe PVD (Note the demarcation after HBOT), a) pre-HBOT, b) Post-HBOT

Case 4: DM with PVD with vasculitis, a) pre-HBOT, b) post-HBOT

Case 5: DM with necrotizing fasciitis: a) pre HBOT, b and c) post-HBOT



Case 6: DM with infected sternal wound (antibiotic beads in situ) a) Pre HBOT, b) Post HBOT

Table 1: Wagner wound grade and response to HBOT.

Response to HBOT	Wagner wound grade		
	2 (n=31)	3 (n=51)	4 (n=30)
Ulcer healed	22	40	11
Ulcer requiring further debridement	9	6	4
Ulcer leading to higher level amputation	0	5	18

Table 2: Result of HBOT in diabetic foot wound with PVD.

Result of HBOT	PVD patients undergoing PAG and Plasty N=55	PVD patients undergoing bypass procedure. N=6	PVD patients were not fit for any kind of vascular intervention. N=20
Ulcer healed	41	5	4
Required further debridement	7	1	3
Required higher level amputation	7	0	16
TcPO2 <40 mm Hg before HBOT	10	2	20
TcPO2 >40 mm Hg after HBOT	48	6	4
TcPO2 <40 mm Hg after HBOT	7	0	16

Table 3: Result of HBOT in diabetic foot wound without significant PVD.

Result of HBOT	Leukocytoclastic vasculitis (n=16)	Necrotizing Fasciitis (n=6)	Burn injury. (n=4)	Venous ulcer N= (5)
Ulcer healed	10	4	3	4
Required further debridement	6	2	1	1
Required higher level amputation	0	0	0	0

Table 4: Total number of patients in whom TcPO2 was measured.

	TcPO2 > 40 mm Hg after HBOT (74)	TcPO2 < 40 mm Hg after HBOT (28)
PVD (81)	58	23
Leukocytoclastic vasculitis (16)	11	5
Venous ulcer (5)	5	0

Table 5: Wound outcome and TcPO2 value (after HBOT)

	TcPO2 > 40mm Hg after HBOT (58) PVD	TcPO2 < 40mm Hg after HBOT (23) PVD	TcPO2 > 40mm Hg after HBOT	TcPO2 < 40mm Hg after HBOT	TcPO2 > 40mm Hg after HBOT	TcPO2 < 40mm Hg after HBOT
	PVD	PVD	(Leukocytoclastic Vasculitis) (11)	(Leukocytoclastic Venous ulcer) (5)	(Venous ulcer) (5)	
Ulcer healed	43	4	8	2	4	0
Required debridement	8	3	3	3	1	0
Required higher level amputation	7	16	0	0	0	0

predict poor outcome. 6 patients who required higher viable and ischemic tissue helping us to predict level of amputation. We did amputation after assessing the level of circulation by duplex Doppler. Need for higher level amputation in these patients (completion of HBOT and TcPO2 >40 mm Hg) should not be considered as failure of HBOT in this setting because in-chamber TcPO2 measurement was not available in our set-up, so it was difficult to predict response of HBOT before start of treatment. Higher level amputation had to be done in 6 out of 89 patients because of development of signs of systemic illness like fever, loss of appetite, increased serum creatinine. If patients had not developed these signs, HBOT and other conservative management would have continued with the hope of healing of ulcer as seen in 68 patients out of 89. 59 patients showed improved TcPO2 (>40 m Hg) after completion of HBOT (Table 4).

Many studies[12,13] have excluded patients with significant PVD and CLI for consideration of HBOT. We have included such patients in our study. We have found that patients showed subjective improvement in pain intensity and frequency.

From the clinical experience at our centre, we can give independent observation that response to HBOT, if at all comes, is visible within the first 7-10 sessions. If after 15 sessions of HBOT there is not a good response in the wound, then that patient will not show response to further sessions. If some delayed response is seen after 15 sessions, it may not be persistent in future and the delayed response is most likely to stay short lived, not sufficient for complete healing of wound. These patients may ultimately require further debridement or higher-level amputation. This observation can be useful where TcPO2 measurement facility is not available for deciding about HBOT.

Another observation from this study useful for clinical practice is that even with TcPO2 >40 mm Hg, few patients in current study still needed further debridement (15 cases) or higher-level amputation (6 cases), (Table 4). This number is quite high. So TcPO2 > 40 mm Hg with or without HBOT does not guarantee healing and TcPO2 as the only objective criteria for determining efficacy of HBOT does not hold true in all patients. We suggest individual clinical assessment of wound and patient during HBOT for determining efficacy of the treatment as decision ultimately rests on clinical judgement. Our aim should be to achieve ulcer free patient and not to achieve TcPO2 >40 mm Hg. The mean number of HBOT sessions in the present study was 29.01. The number of cases is relatively high, and the follow-up period is sufficient. The study group consisted of consecutive patients admitted to our clinic.

HBOT may cause some complications such as oxygen toxicity in the brain or lung and barotraumas in the middle ear. In the current study we did not observe any permanent complications or patient compliance problems. The patients experienced some mild side

effects like ear blockage, temporary hearing difficulty after HBOT session which resolved after first few sessions.

The present study has some weak points. The most important is the absence of a control group. Thus, randomization could not be realized. Moreover, strict conclusions regarding patients in whom HBOT will not be useful could not be drawn. We know that HBOT can be useful in various diabetic foot wounds, but which patients will benefit cannot be predicted though TcPO2 measurement after completion of HBOT can be a useful indicator.

Out of 89 patients who showed TcPO2 >40 mm Hg at the end of HBOT sessions, 30 patients had TcPO2 > 40 mm Hg to begin with (before start of HBOT), (Table 4). Ulcer response to HBOT in this subgroup needs to be evaluated by a greater number of patients. In this study, the major amputation rates were decreased with adjunctive HBOT therapy in addition to standard treatments and the major amputation rates are compatible with the literature[14,16]. It appears that HBOT is effective in the treatment of diabetic foot ulcers, nevertheless, this treatment cannot be considered a substitute for standard treatments and is to be accepted as adjunctive therapy.

CONCLUSIONS

HBOT can be useful adjunctive treatment in a wide spectrum of diabetic foot wounds. However, it is difficult to predict which patients will show positive response and which patients are not candidates for HBOT. If patient is clinically fit to undergo HBOT, then HBOT can be considered as an adjunct to standard care in all chronic non-healing wounds.

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