SCIE DOI: 10.14744/scie.2018.57070
South. Clin. Ist. Euras. 2018;29(4):258-261

Original Article

Evaluation of Hyperbaric Oxygen Therapy in the Management of Diabetic Foot Ulcers

Ayşe Serra Özel, Lütfiye Nilsun Altunal, Zeynep Şule Çakar, Merve Çağlar Özer

Department of Infectious Diseases and Clinical Microbiology, University of Health Science, Ümraniye Training and Research Hospital, İstanbul, Turkey

Submitted: 15.08.2018
Accepted: 24.09.2018

Correspondence: Ayşe Serra Özel, SBÜ Ümraniye Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Kliniği, İstanbul, Turkey
E-mail: aserra.ozel@gmail.com

Keywords: Amputation; diabetic foot ulcer; hyperbaric oxygen therapy.

ABSTRACT

Objective: Hyperbaric oxygen therapy (HBOT) is a medical treatment method that involves sessions of breathing 100% oxygen, and it is a commonly used supportive therapy for patients with diabetic foot ulcer (DFU). The present study aimed to evaluate the efficacy of HBOT in patients with DFU.

Methods: Among DFU patients followed-up between 2016 and 2018 at a single hospital, 30 patients who underwent HBOT and 42 patients who did not were randomly selected and the epidemiological and clinical characteristics of both groups, as well as the clinical outcomes of the patients at the end of treatment were compared.

Results: Twenty-six patients (86.7%) in the HBOT group and 14 patients (33.3%) in the non-HBOT group were classified as PEDIS score 3–4 (p=0.000). The rate of re-hospitalization was significantly higher in the HBOT group (p=0.005). The rate of major and minor amputations were found to be similar in both groups, but it was more likely to be distally located in the HBOT group (p=0.035 vs. p=0.128).

Conclusion: The greater rate of re-hospitalization and need for surgical intervention in the HBOT group may have been related to the presence of advanced stage DFU. The amputation rate was similar in both groups. Randomized, prospective, multicenter studies are needed to further evaluate HBOT efficacy.

INTRODUCTION

Diabetic foot ulcer (DFU) is among the most common complications related to diabetes and leads to a decrease in the quality of life of patients, as well as increased mortality and morbidity rates and health care costs.[1] The prevalence of diabetic patients is increasing rapidly all over the world. Currently, there are approximately 382 million diabetic patients worldwide and approximately 316 million with impaired glucose tolerance.

As of 2035, the number of patients with diabetes is estimated to reach 471 million.[2] According to Ministry of Health data, there are some 7 million diabetes patients in Turkey,[3] and more than 1 million with DFU and 500,000 with a diabetic foot infection. This represents a substantial cost to the country, and it is expected to increase in the coming years.[4]

DFU may appear as an ulcer, infection, or foot deformity in the presence of peripheral arterial disease (PAH) or neuropathy.[5] The presence of PAH or neuropathy leads to rapid progression in DFUs, including the development of deep tissue or bone infection and the necessity for lower extremity amputation.[6,7] The approach in the treatment of DFU is management of infection and metabolic control. Hyperbaric oxygen therapy (HBOT) increases oxygenation in hypoxic wound tissue, as well as angiogenesis, fibroblast activation, and increased collagen production, and can accelerate healing in cases of DFU.[8] The aim of this study was to evaluate the effect of HBOT on wound healing and amputations in the treatment of DFU.

MATERIAL AND METHODS

Among DFU patients who were followed-up in a single hospital between 2016 and 2018, 30 who underwent HBOT treatment and 42 who did not receive HBOT were included in this study. Patients were randomly selected from DFU follow-up forms and the epidemiological and clinical characteristics of both groups as well as the clinical outcomes at the end of the treatment were compared.

The details of patient age; gender; duration of diabetes and DFU; level of glycated hemoglobin (HbA1c) at admission; any history of amputation; stage of PAD, neuropathy, or infection; presence of osteomyelitis (OM); previous surgical interventions; presence of arterial flow disorder observed on Doppler ultrasound; white blood cell (WBC) count; C-reactive protein (CRP) level; and erythrocyte sedimentation rate (ESR) were recorded.

Table 1. Clinical and epidemiological characteristics

	HBOT (+) (n=30)	HBOT (–) (n=42)	p
Age (years)*	59.4 (32–77)	65.9 (41–88)	0.006
Male	21 (70%)	24 (57.1%)	0.231
Duration of diabetes (years)*	14.1 (0–33)	14.1 (2–40)	0.516
HbA1c*	9 (6.5–14.2)	9.1 (5.4–16)	0.820
Duration of DFU*	87.6 (2–365)	54 (2–720)	0.284
History of amputation	22 (73%)	36 (87.8%)	0.471
Stage 2–3 PAD	22 (73.3%)	30 (73.2%)	0.257
Stage 2 neuropathy	21 (84%)	35 (83.3%)	0.515
Stage 3–4 PEDIS	26 (86.7%)	14 (33.3%)	0.000
Impaired arterial circulation	18 (75%)	12 (54%)	0.815
History of surgical intervention	22 (75%)	7 (17%)	0.004
Osteomyelitis	11 (36%)	8 (25.8%)	0.561
White blood cell count*	10847 (4100–25400)	9415 (4890–19400)	1.0
C-reactive protein*	6.6 (0.2–25.9)	5 (10–26.5)	0.475
Erythrocyte sedimentation rate*	57.8 (19–91)	46 (6–102)	0.791

*Mean; HBOT (+): Patients who underwent HBOT; HBOT (–) Patients who did not receive HBOT. DFU: Diabetic foot ulcer; HbA1c: Glycated hemoglobin; HBOT: Hyperbaric oxygen therapy; PAD: Peripheral artery disease.

Table 2. Clinical outcomes of the treatment

	HBOT (+) (n=30)	HBOT (–) (n=42)	p
Level of amputation**	3 (1–6)	4.6 (2–6)	0.035
Re-hospitalization	11 (36%)	0 (0%)	0.005
Follow-up period (days)*	67.8 (3–810)	32 (1–360)	0.410
Recovery	4 (22.2%)	24 (85.7%)	0.128
Minor amputation	11 (61.1%)	2 (7.1%)	0.128
Major amputation	3 (16.7%)	2 (7.1%)	0.128

*Mean; **Level of amputation: 1. Big toe; 2. Other toes; 3. Metatarsal level; 4. Ankle; 5, Below the knee; 6. Above the knee. HBOT (+): Patients who underwent HBOT; HBOT (–) Patients who did not receive HBOT.

In addition, the clinical outcomes of both the patients who underwent HBOT and those who did not, the amputation level (major or minor), need for re-hospitalization, follow-up period (days), and details of wound healing were documented.

Infection, wound depth, sensory loss (neuropathy) and the PAD stage of foot lesions were defined according to the PEDIS classification.[9] The diagnosis of OM was based on the presence of luminal lesions and periosteal reaction observed on plain radiographs or bone involvement seen in magnetic resonance imaging.

Statistical method

The collected data were analyzed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Fisher's exact test and chi-square tests were used to compare ratios, while non-normal parametric data were analyzed using the Mann-Whitney U test. P<0.05 was considered statistically significant.

RESULTS

A total of 30 DFU patients who underwent HBOT and 42 who did not were included in the study. Comparison of the groups revealed that HBOT was applied more frequently in young patients (p=0.006).

The duration of diabetes; HbA1c level; history of amputation; presence of stage 2 2-32 PAD, stage 2 neuropathy, or OM; and ESR, CRP, and WBC levels were similar in both groups.

A history of surgical intervention (debridement, abscess drainage, vascular intervention, etc.) was significantly greater in the HBOT group (p=0.004). In the HBOT group, 26 patients (86.7%) were classified as PEDIS grade 3-4, while there were 14 patients (33.3%) in the non-HBOT group with the same classification (p=0.000) (Table 1).

When the final clinical results of both groups were evaluated, the rate of re-hospitalization was significantly greater in the HBOT group (p=0.005). The rate of major and minor amputations was similar in both groups (p=0.128).

DISCUSSION

The gold standard in the management of DFU is regulation of blood sugar, treatment of infection, revascularization, debridement, and reduction of weight bearing on foot. HBOT, wound care products, and negative pressure wound therapies are recommended as supportive treatment.[10] HBOT is the administration of 100% oxygen in a high pressure chamber at a pressure of 2 to 3 atmospheres absolute for daily sessions of 2 to 3 hours.[11]

HBOT typically includes 30 sessions, and can be extended to as many as 90 sessions, depending on the condition of

the patient's wound. The goal of HBOT is to accelerate wound healing by reducing regional and local ischemia. Increased oxygen pressure in hypoxic tissues causes fibroblast proliferation and angiogenesis and decreases edema in tissue through vasoconstriction. In addition, a decrease in pro-inflammatory cytokines augments the bacteria-killing effect of leukocytes and decreases inflammation.[12]

It has been established that HBOT is particularly effective in patients with palpable pulses and no major vessel damage.[13] Numerous studies have investigated the effects of HBOT, which is now accepted for use at many centers and is beginning to be used in the management of DFU. The first randomized controlled trial was conducted by Doctor et al.[14] It was demonstrated that the group that underwent HBOT had fewer major amputations, but more minor amputations. HBOT was reported to be an effective and reliable adjunctive treatment option in cases of DFU.

Randomized clinical studies have also been conducted. The application of HBOT with standard therapies has been shown to lead to a decrease in major amputations and an increase in wound healing.[15,16]

Stage 2-3 PAD was most frequent among our study patients and there was no significant difference between the major and minor amputation rates between the HBOT group and the non-HBOT group. This result was consistent with two similar randomized, double-blind, placebo-controlled trials involving ischemic ulcers.[8,17]

In a meta-analysis of 526 patients performed by Zhao et al.[18] that included 9 randomized clinical trials, it was reported that HBOT did not reduce the rate of major or minor amputations, but significantly reduced the size of ulcers. In another study of ischemic ulcers, there was no decrease in major amputation rates, but a significant increase in the minor amputation rate was seen in the HBOT group.[19]

The fact that the definitions of major and minor amputations used in the studies presents a difficulty in comparing studies. In our study, although the amputation rates were not different between the 2 groups, the site of the amputation was observed more frequently to be distally located in the HBOT group (p=0.035). This finding may be explained by the greater incidence of surgical intervention in the group that underwent HBOT (p=0.04) and an increase in tissue oxygenation, which accelerates wound healing.

In our study, no significant difference was found between the HBOT and non-HBOT groups in terms of ulcer healing. In many other studies, however, HBOT has been shown to promote ulcer healing.[17,20,21] This may be explained by the fact that there were more stage 3-4 PEDIS ulcers in the HBOT treatment group and the patients' clinical status was more severe.

It has been suggested that the rate of re-hospitalization and the need for surgical intervention in patients receiving HBOT may be related to the progression of infection.

There are some limitations to our study. HBOT causes an increase in oxygenation of the blood circulation in both legs. No information could be obtained about the development of ulcers or the need for amputation in the other leg could be determined in the follow-up data of our study.

The patient data were retrospectively obtained from diabetic foot follow-up forms and the hospital registry system. Furthermore, it was not possible to evaluate how well the patients adapted to HBOT. Finally, the patients' microbiological factors and the duration of antibiotic treatment were not taken into consideration.

CONCLUSION

HBOT is a supportive treatment that is frequently used in many clinics for the treatment of DFU. Larger, prospective, randomized, multicenter studies are needed to further evaluate the effectiveness of HBOT in cases of DFU.

Ethics Committee Approval

This was a retrospective study, therefore no ethics committee approval was taken.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: A.S.Ö.; Design: A.S.Ö.; Data collection &/or processing: M.Ç.Ö.; Analysis and/or interpretation: Z.Ş.Ç., A.S.Ö.; Literature search: L.N.A.; Writing: A.S.Ö.; Critical review: A.S.Ö.

Conflict of Interest

None declared.

REFERENCES

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719–24.
2. International Diabetes Federation. Diabetes Atlas. 8th ed. 2017. Available at: http://www.idf.org/diabetesatlas. Accessed Nov 19, 2018.
3. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, et al; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013;28:169–80.
4. Saltoğlu N, Kılıçoğlu Ö, Baktıroğlu S, Oşar-Siva Z, Aktaş Ş, Altındaş M, et al. Diyabetik Ayak Yarası ve İnfeksiyonunun Tanısı, Tedavisi ve Önlenmesi, Ulusal Uzlaşı Raporu. Klimik Dergisi 2015;28:2–34.
5. Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K; International Working Group on the Diabetic Foot. Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev 2016;32:7–15.
6. Martins-Mendes D, Monteiro-Soares M, Boyko EJ, Ribeiro M, Barata P, Lima J, et al. The independent contribution of diabetic foot ulcer on lower extremity amputation and mortality risk. J Diabetes Complications 2014;28:632–8.
7. Saltoglu N, Yemisen M, Ergonul O, Kadanali A, Karagoz G, Batirel A, et al; KLIMIK Turkish Society, Diabetic Foot Study Group. Pre-

dictors for limb loss among patient with diabetic foot infections: an observational retrospective multicentric study in Turkey. Clin Microbiol Infect 2015;21:659–64.
8. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010;33:998–1003.
9. The International Working Group on the Diabetic Foot. International consensus on diagnosing and treating the infected diabetic foot. 4th International symposium on the diabetic foot. May 22–24, 2003. Noordwijkenhout-The Netherlands. 2003.
10. Alexiadou K, Doupis J. Management of diabetic foot ulcers. Diabetes Ther 2012;3:4.
11. Barnes RC. Point: hyperbaric oxygen is beneficial for diabetic foot wounds. Clin Infect Dis 2006;43:188–92.
12. Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration. Surgery 1981;90:262–70.
13. Weisz G, Ramon Y, Melamed Y. Treatment of the diabetic foot by hyperbaric oxygen. Harefuah 1993;124:678–81.
14. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. J Postgrad Med 1992;38:112–4.
15. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. PM R 2009;1:471–89.
16. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2004;CD004123.
17. Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg 2003;25:513–8.
18. Zhao D, Luo S, Xu W, Hu J, Lin S, Wang N. Efficacy and Safety of Hyperbaric Oxygen Therapy Used in Patients With Diabetic Foot: A Meta-analysis of Randomized Clinical Trials. Clin Ther 2017;39:2088–94.
19. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. Diabetes Care 1996;19:1338–43.
20. Kessler L, Bilbault P, Ortéga F, Grasso C, Passemard R, Stephan D, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care 2003;26:2378–82.
21. Ma L, Li P, Shi Z, Hou T, Chen X, Du J. 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 2013;59:18–24.

Hiperbarik Oksijen Tedavisinin Diyabetik Ayak Ülserleri Üzerinde Etkinliğinin Değerlendirilmesi

Amaç: Hiperbarik oksijen tedavisi (HBOT), hastaya aralıklı olarak %100 oksijen solutularak uygulanan medikal bir tedavi yöntemi olup diyabetik ayak ülseri (DAÜ) olan hastalarda yaygın olarak kullanılan destekleyici bir tedavi yöntemidir. Çalışmamızda DAÜ olan hastalarda HBOT'nin etkinliğinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Hastanemizde 2016–2018 yılları arasında takip edilmiş HBOT alan 30 hasta ve HBOT almayan 42 hasta rastgele olarak seçildi, her iki grubun epidemiyolojik, klinik özellikleri ve hastaların tedavi bitiminde klinik sonuçları karşılaştırıldı.

Bulgular: Hiperbarik oksijen tedavisi alan grupta 26 hasta (%86.7), almayan grupta 14 hasta (%33.3) PEDIS 3–4 idi (p=0.000). HBOT alan grupta yeniden hastaneye yatış oranlarının anlamlı olarak daha fazla olduğu görüldü (p=0.005). Majör ve minör amputasyon ile sonuçlanma oranları her iki grupta benzer olmakla birlikte HBOT alan grupta amputasyon seviyesinin almayan gruba göre daha distalde olduğu görüldü (p=0.035 ve p=0.128).

Sonuç: Çalışmamızda HBOT alan grupta hastaların tekrar hastaneye yatış oranının ve cerrahi girişim ihtiyacının daha fazla olmasının bu hastalarda DAÜ'nün ileri evrede olması ile ilişkili olabileceği düşünülmüştür. Her iki grupta amputasyon oranları benzer olup HBOT etkinliğinin değerlendirilmesi için daha fazla sayıda randomize, plasebo kontrollü çok merkezli çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: Amputasyon; diyabetik ayak ülseri; hiperbarik oksijen tedavisi.