Hyperbaric oxygen treatment in thromboangiitis obliterans: a retrospective clinical audit

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Key words
Buerger's disease; Chronic wounds; Pain; Outcome

Abstract
(Hemsinli D, Altun G, Tuba Kaplan S, Yildirim F, Cebi G. Hyperbaric oxygen therapy in thromboangiitis obliterans: a retrospective clinical audit. *Diving and Hyperbaric Medicine*. 2018 March;48(1):31–35. doi:10.28920/dhm48.1.31-35. PMID: 29557099.)
Introduction: Wounds refractory to standard treatment in patients with thromboangiitis obliterans (TAO, Buerger's disease) are associated with amputation, other morbidity and mortality. The purpose of this study was to investigate the effect of hyperbaric oxygen treatment (HBOT) in patients with TAO.
Materials and methods: Ninety-seven patients with TAO with ischaemic wounds treated between January 2007 and July 2016 were included in this dual-centre, non-randomised, retrospective study. Patients receiving HBOT in addition to conventional treatment were enrolled in an HBOT group (n = 47) and those receiving conventional treatment alone in a non-HBOT group (n = 50). All patients were Rutherford grade III at the time of enrolment.
Results: Significant improvement in the major amputation rate was observed in the HBOT group 10 months after starting treatment (2/47 vs. 13/50, P = 0.007). Numbers of patients progressing to Rutherford grade I (27/47 vs. 17/50, P = 0.035), numbers of patients healing completely (21 vs. 11, P = 0.031 and pain scores (visual analogue scale; 1, range 0–8 vs. 6, range 0–9, P < 0.001) were also significantly improved in the HBOT group.
Conclusion: The addition of HBOT to conventional treatment in TAO patients with non-healing ischaemic wounds and severe extremity pain, conferred significant benefits in terms of wound healing and rest pain control. Multi-centre, prospective, randomized studies with blinded outcome analysis are now needed to elicit more reliable results.

Introduction

Thromboangiitis obliterans (TAO, Buerger's disease) is a non-atherosclerotic, segmental, inflammatory disease of uncertain etiology affecting the small and medium-sized vessels in the extremities. The prevalence of the disease among all patients with peripheral arterial disease ranges from as low as 0.5–5.6% in Western Europe to as high as 45–63% in India, 16–66% in Korea and Japan and 80% amongst Jews of Ashkenazi ancestry living in Israel. A powerful association exists between smoking and the inflammatory process involved in the onset and progression of the disease.[1,2]

The pathological process that begins with hypercellular and inflammatory thrombus formation in TAO concludes with occlusion in the distal vascular bed and tissue hypoxia. Clinical symptoms begin with claudication, followed by severe rest pain and ischaemic wounds (IWs) caused by tissue necrosis as the disease progresses.[1,2] Severe rest pain and IWs in TAO cause social problems and workforce losses and thus have an adverse impact on daily life. Standard treatments include revascularization techniques and agents such as acetylsalicylic acid, pentoxifylline, clopidogrel, cilostazol and intravenous iloprost infusion. IWs, many of which do not heal with standard treatment methods, also provoke secondary diseases, such as infection and organ dysfunction. Non-healing wounds have a high risk of leading to amputation, which is in turn associated with other morbidity, mortality and increased treatment costs.[1–5]

Surgical revascularization in patients with TAO is generally not possible due to distal and diffuse segmental occlusion in the extremity arteries. In addition, the benefits of bypass surgery are questionable due to high graft failure rates. However, bypass surgery may be considered in the presence of a suitable distal vessel bed in patients with severe ischaemic findings.[1,2,6,7] Surgical revascularization is reported to have been possible in only 21 out of 216 patients and that patency levels were not promising.[1] Studies have

emphasized that smoking cessation is the most successful method of treating TAO, and that all other methods are palliative.[1,2,6,7]

Several studies have shown that hyperbaric oxygen treatment (HBOT) significantly accelerates healing in IWs, increases oxygen flux in the wound area and reduces the tendency to necrosis in the extremity.[8,9] However, almost all the literature consists of studies involving diabetic or atherosclerotic patients.[8–10] In a series of 36 patients with TAO and IWs,[11] we concluded that the patients' clinical condition improved significantly with HBOT and that it was easier for them to perform their daily activities. Both pain and wound area were significantly better ($P < 0.001$ for both.[11] These findings constituted useful evidence for the use of HBOT in the treatment of IWs in TAO. However, the small number of patients and lack of a control group limit the value of these clinical results. As a result, we performed a larger dual-centre retrospective clinical audit. The main outcome criterion was improvement in the major amputation rate at the tenth month after initiation of treatment. Secondary outcomes were improvement in Rutherford grade, healing of IWs and pain scores at 10 months.

Materials and methods

A dual-centre, non-randomised, comparative, retrospective study was performed with the approval of the local ethics committee and in line with the Declaration of Helsinki. The archive records of patients treated and monitored with a diagnosis of TAO at the Karadeniz Technical University Medical Faculty and Health Sciences University Kanuni Training and Research Hospital, Turkey between January 2007 and July 2016 were reviewed. Data were obtained from the archive records, clinical follow-ups and telephone interviews with physicians. One-hundred-thirteen patients diagnosed with TAO on the basis of clinical and radiological findings and with IWs of the extremities were identified. Sixteen patients were excluded: one with osteomyelitis based on magnetic resonance imaging; four whose records were missing; two unable to receive HBOT owing to claustrophobia; five with chronic obstructive lung disease and four with an ejection fraction < 35%. Following exclusions, all patients included for analysis in this study commenced as Rutherford grade III prior to intervention.

The Rutherford classification is widely used in cardiovascular surgery departments to evaluate the severity of peripheral vascular diseases. In this classification, grade 0 is used to define asymptomatic patients, grade I for patients with claudication (mild, moderate, severe), grade II for patients with ischaemic rest pain, and grade III for patients with ulcers, gangrene or tissue loss.[12]

Based on these criteria, data from 97 patients with severe ischaemic rest pain and infected ischaemic ulcers in the extremities were analyzed. The HBOT group (n = 47) which included the 36 patients from the previous study consisted of patients receiving HBOT in addition to standard treatment methods. The non-HBOT group (n = 50) consisted of patients not receiving HBOT. Reasons for not receiving HBOT included non-availability of a hyperbaric physician and the fact that the hyperbaric medicine unit did not open until 2010.

HBOT was administered in a multiplace chamber (Hiperbot Model 101, 2005, Turkey) allowing 12 patients to be treated simultaneously. The chamber was pressurized with medical air to 240 kPa (2.37 ATA) over 15 minutes (min), then patients received three sessions of 100% oxygen by mask for 30 min, each session separated by a 5-min air break and decompression was over 10 min. HBOT was administered five days a week for the duration of hospital stay. All patients were accompanied by a member of the medical staff during HBOT. After discharge from hospital, patients received HBOT only when clinically indicated.

All patients received standard medical treatment consisting of acetylsalicylic acid, pentoxifylline, clopidogrel and cilostazol. Patients without an ejection fraction < 40% and/or New York Heart Association (NYHA) heart failure class 3–4 were started on intravenous iloprost at 0.5 $ng \cdot kg^{-1} \cdot min^{-1}$ (Ilomedin, Bayer-Schering AG, Germany) for six hours per day for 21 days. On the first day, the dose was increased by 0.5 $ng \cdot kg^{-1} \cdot min^{-1}$ every half hour to a maximum of 2 $ng \cdot kg^{-1} \cdot min^{-1}$. If any side effects appeared, the dose was reduced back to the preceding one. Empiric antibiotic therapy was started after culturing the wound and was revised according to the culture results. When necessary, aggressive debridement or amputation was performed on the extremity containing the wound, followed by wound care and dressings. The dressings were changed at frequent intervals and wounds were protected from uncontrolled mechanical pressure.

Patients' clinical status and severity of peripheral vascular disease were evaluated using Rutherford's criteria at admission, and 10 months after commencing treatment, either HBOT or the initial treatment of non-HBOT patients.[12] Vascular lesions were classified according to Graziani's morphological classification (data not reported here).[13] At 10 months, cases were classified as complete healing (no infection in the wound, no necrotic tissue, adequate granulation tissue formation and completion of epithelialization) or incomplete healing (infection in the wound or presence of necrotic tissue or inadequate granulation tissue or incomplete epithelialization). The location and size of IWs were recorded at admission, at discharge, and during outpatient visits in case of incomplete healing at discharge. The areas of IWs were obtained from patient records, and was calculated by multiplying the longest and widest dimensions.

Severity of ischaemic extremity pains was evaluated using a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain). Pain-free walking

Table 1
Baseline characteristics of the patient population (number or median and range); HBOT – hyperbaric oxygen treatment; VAS – visual analogue scale; 25 patients in the HBOT group and 17 patients in the non-HBOT group

	HBOT (n = 47)	Non-HBOT (n = 50)
Females/Males	1/46	1/49
Age (years)	50 (32–68)	45(37–75)
Smoker	44	48
Thrombophlebitis migrans	7	9
Previous sympathectomy	20	23
Previous surgical revascularization	5	6
Previous endovascular therapy	4	4
Upper extremity involvement	5	7
Previous minor amputation	12	15
Previous major amputation	8	6
IW area (cm^2)	21 (5–70)	15 (2–45)
VAS score	8 (5–9)	8 (5–9)
Rutherford grade III	All	All

Table 2
Outcomes at 10 months (number or median (range); HBOT – hyperbaric oxygen treatment; VAS – visual analogue scale; * P = 0.007; † P = 0.031; ‡ 0.0043; § P < 0.001; ** owing to incomplete healing and amputation

	HBOT (n = 47)	**Non-HBOT** (n = 50)
Major amputation *	2	13
during hospitalization	1	6
during follow-up	1	7
Complete healing †	21	11
Rutherford grade ‡		
I	27	17
II	5	10
III	15	23
Wound area (cm^2)	12 (0–60)	11 (0–45)
VAS score §	1 (0–8)	6 (0–9)
Pain-free walking (m) **	200 (40–500)	200 (100–200)
Hospitalization (days)	60 (30–120)	60 (60–120)
Mortality at 10 months	1	1

distances were measured only in patients who had not undergone major amputation and with a Rutherford grade < II. Demographic variables such as smoking status and duration, pain characteristics, previous surgical interventions (sympathectomy, peripheral revascularization procedures, minor/major amputation), endovascular therapy, medical treatments received for TAO, complications and mortality were recorded during treatment and follow-up.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) 23.0 software was used for data analysis. Normality of distribution was examined using the one-sample Kolmogorov-Smirnov test. Results were expressed as mean (standard deviation) for normal data (age), median (range) for non-normal data (duration of follow-up, IW area, VAS, duration of hospitalization, pain-free walking distance), and median values for Rutherford classifications, and as number for categoric data (gender, smoking status, thrombophlebitis migrans, surgical interventions, complete healing, and Rutherford class). Comparison of numerical variables between two independent groups was performed using the Mann Whitney U test since normal distribution was not established. The chi square test was used to analyze differences between ratios of categoric variables in independent groups. $P < 0.05$ was regarded as statistically significant.

Results

Ninety-seven patients, presenting with IW and Rutherford grade III diagnosed with TAO were included in the final analysis (Table 1). Briefly, both groups were similar in terms of age, severity of disease, and comorbidities such as smoking status and previous surgical procedures. There were no statistically significant differences in terms of medical treatments or smoking cessation between the HBOT and non-HBOT groups. No procedure-related complications occurred in any patient.

Patients in the HBOT group were followed up for a median of 30 (range 10–48) months and those in the non-HBOT group for 23 (range 10–48) months (P = 0.071). The 10-month follow-up data are summarised in Table 2. During this period, patients in the HBOT group received a median of 34 sessions (range 10–62). The incidence of minor amputation (amputation leaving sufficient functional foot to permit the patient to walk without prosthesis) was similar in both groups (19 vs 30, P = 0.084). However, the number of major amputations (patients with Syme's amputation, above or below knee amputation) was significantly lower in the HBOT group (2 vs. 13, P = 0.007). Significantly more patients in the HBOT group were completely healed at 10 months (21 vs. 11, P = 0.031) and VAS scores were lower in the HBOT group. Median post-treatment Rutherford grade was 1 (range 1–3) in the HBOT group, and 2 (range 1–3) in the non-HBOT group (P = 0.043); more patients in the HBOT group improved to grade I. IW area did not differ significantly, and duration of hospitalization was similar in the two groups.

Discussion

This study shows that the addition of HBOT to conventional medical treatment of TAO reduced the number of major amputations, improved the Rutherford grade, the rate of healing of IWs and VAS scores at 10 months from the initiation of treatment for both groups.

The healing of IWs represents the most critical stage in terms of preventing amputation.[9,14,15] Therefore, adjuvant therapeutic options such as HBOT, capable of contributing to wound healing and preventing amputation in TAO patients with IWs, are important. A literature review revealed no previous studies on HBOT in the treatment of TAO patients with IWs apart from our own.[11] One study reported an 11% risk of major amputation (above the knee, below the knee or hand amputation) at five years, 21% at 10 years and 23% and 20 years in TAO patients treated using conventional methods.[16] In our study, there were 13 major amputations in 50 patients (26%) in the non-HBOT group. We attribute the higher level of amputation in the non-HBOT group to all the patients being Rutherford grade III at entry, in contrast to the previous study.

HBOT has been shown to act both locally and systemically. Locally, it increases several growth factors, such as vascular endothelial growth factor (VEGF) and nitric oxide (NO) involved in angiogenesis in ischaemic tissue,[17] and enhances diffusion gradients for oxygen into the wound. In addition, HBOT reduces capillary pressure and transcapillary fluid transfer and increases extravascular fluid absorption, thus reducing lower extremity oedema. Systemically, it stimulates the release of bone marrow progenitor stem cells,[18] decreases circulating inflammatory cytokines and increases fibroblastic activity, collagen production and the efficacy of antibiotics.

Despite the limited studies of the efficacy of the different methods used to treat TAO, some studies have elicited promising results. Applying vascular endothelial growth factor improved wound healing in four out of six patients with IWs and increased collateral vascularization around the injection site in five of the seven subjects.[17] Autologous bone marrow transplantation in seven TAO patients with ischaemic extremities, combined with four sessions of HBOT two days before transplant, then one day, two and four weeks after transplant, resulted in significant improvement in pain and walking distances compared to the pre-treatment period.[3]

The improvement in VAS values was more marked than in our previous single-cohort study of 36 patients in whom the mean VAS score was 7.1 (SD 1.7) before HBOT compared to 2.2 (3.0) after treatment ($P = 0.0001$).[11] We attribute this to patients newly included in the study having lower pain scores after treatment compared to those from the previous study. One patient who died and two who underwent major amputation in the HBOT group, and one patient who died and 13 who underwent major amputation in the non-HBOT group had continued to smoke. This demonstrates the importance of smoking cessation as part of the overall management of these patients.

LIMITATIONS

The principal limitations of this study are that it is non-randomised, retrospective and the patient numbers are limited. Also, only a short (10 months) follow up was undertaken. However, the fact that no consensus has been achieved concerning treatment protocols for TAO and that the disease is relatively rare make it difficult to perform large, prospective, randomized studies of these patients.

Conclusions

The addition of HBOT to standard treatment methods in patients with TAO with non-healing IWs and severe extremity pain appears to provide significant benefits in terms of the rate of major amputation, healing of IWs and control of rest pain. Multi-centre, prospective randomized studies with blinded outcome analysis are now needed to elicit more reliable results.

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Funding and conflicts of interest: nil

Submitted: 16 July 2017; revised 17 October 2017 and 17 January 2018
Accepted: 28 January 2018
