International Journal of Dermatology

Clinical trial

A prospective randomized controlled trial assessing the efficacy of adjunctive hyperbaric oxygen therapy in the treatment of hidradenitis suppurativa

Hamza Yildiz[1], MD, Levent Senol[2], MD, Erdinc Ercan[3], MD, Memet Ersan Bilgili[4], MD, and Ozlem Karabudak Abuaf[5], MD

[1]Department of Dermatology, Eskisehir Military Hospital, Eskisehir, Turkey, [2]Turkish Air Force Aeromedical Research and Training Center, Eskisehir, Turkey, [3]Department of Hyperbaric Medicine, Eskisehir Military Hospital, Eskisehir, Turkey, [4]Department of Dermatology, Yunus Emre State Hospital, Eskisehir, Turkey, and [5](retired from) Department of Dermatology, Gata Haydarpasa Teaching Hospital, Istanbul, Turkey

Correspondence
Hamza Yıldız, MD
Department of Dermatology
Eskisehir Military Hospital
Eskisehir 26010
Turkey
E-mail: hamzayildiz@gmail.com

Conflicts of interest: None.

Abstract

Hyperbaric oxygen therapy (HBOT) appears to enhance wound healing, increase bactericidal activity, and act synergistically with a number of antibiotics. The aim of this study was to evaluate the efficacy of HBOT as an adjunctive therapy in patients with hidradenitis suppurativa (HS) treated with a combination of systemic rifampicin and clindamycin. The study was a prospective, single-center, single-dose, open-label, randomized controlled clinical study of HBOT in patients with moderate to severe HS. Efficacy was measured by modified Sartorius score (SS), HS Severity Index (HSSI), Dermatology Life Quality Index (DLQI), and a visual analog scale (VAS) before treatment and after the completion of 4 and 10 weeks of treatment. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were also measured. Forty-three patients were enrolled in the study. More patients in the HBOT than in the control group showed a decrease of ≥50% from baseline parameters at week 10 for SS (100%), HSSI (100%), DLQI (95.5%), VAS (100%), ESR (100%), and CRP (72.7%). Clinically and statistically significant improvements from baseline were observed at 4 and 10 weeks in HSSI ($P = 0.009$ at both), SS ($P = 0.021$ at both), and DLQI ($P = 0.044$ at week 4, $P = 0.009$ at week 10). Adjunctive HBOT was considered to be effective in significantly improving antibiotic treatment of HS. The treatment was well tolerated, and no unexpected safety issues were identified.

Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease characterized by recurrent, painful abscesses and nodules primarily in intertriginous areas.[1–3] The first line of treatment for stage 1 and 2 HS combines rifampicin with either oral clindamycin or minocycline,[4] resulting in remission in about 75% of cases.[5] Because of its wound-healing, anti-hypoxic, anti-edema, and anti-infective properties,[6] we speculated that hyperbaric oxygen therapy (HBOT) might help to increase antibiotic treatment efficacy.

The aim of this study was to evaluate the efficacy of HBOT as an adjunctive therapy in patients treated with a combination of rifampicin and clindamycin.

Materials and methods

The study was a prospective, single-center, single-dose, open-label, randomized controlled clinical study of HBOT in patients with moderate to severe HS. Ethical approval was obtained from Eskisehir Osmangazi University Clinical Research Ethics Committee (March 29, 2012; protocol no. 2012/66). The study protocol complied with the ethical guidelines of the Declaration of Helsinki of the World Medical Association.

Patients

Patients who were diagnosed with HS in the Department of Dermatology at the secondary State Hospital, Eskisehir, Turkey, between April 2012 and July 2014 participated in the study. The patients were divided into two groups. The first group of patients ($n = 22$) was treated with antibiotics and HBOT (HBOT group). The second group of patients ($n = 21$) was treated with antibiotics only (control group).

Only patients aged >18 years were included in the study. Criteria for exclusion from HBOT were pregnancy, pneumothorax, severe chronic obstructive pulmonary disease, recent chest surgery, upper or lower airway infection, psychiatric problems (especially claustrophobia), concussion or head injury, convulsions, epilepsy, and heart disease (ejection fraction <35).

At the first visit, a standardized form was used to record demographic characteristics (age, sex), smoking habits, history of disease, and family history of HS. Body mass index (BMI) was computed for all patients, and the anatomic zones affected were identified and recorded with descriptions of typical lesions.

All patients underwent laboratory and radiographic evaluations including a blood cell count and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), renal and liver function profiles, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV), human immunodeficiency virus (anti-HIV), chest x-ray, and Water's view (occipito-mental) x-ray. Blood cell count and differential, CRP, ESR, and renal and liver function profiles were repeated at the end of weeks 4 and 10.

Treatment

Patients who accepted medical treatment with the combination of clindamycin (300 mg orally, twice per day, taken with food) and rifampicin (300 mg orally, twice per day, taken on an empty stomach) were included in the study. All patients received this therapy for 10 weeks.

Some patients were randomly assigned to treatment with HBOT. Patients in the control group were referred to the hyperbaric medicine department for consideration. Patients were evaluated for contraindications for HBOT, and informed consent was obtained from patients before HBOT was initiated. Treatment sessions were administered in a multi-place hyperbaric chamber five days per week for four weeks (20 treatment sessions, once per day except at weekends). An HBOT session lasted 120 minutes and included a period of compression in air for 20 minutes, followed by treatment at 2.4 atmospheres absolute (ATA) for three periods of 25 minutes separated by two 5-minute air breaks (mask off), followed by a decompression period of 15 minutes.

Clinical evaluation

Hurley's staging system is simple and relies on the subjective evaluation of the diseased tissue.[1] The Sartorius score (SS)[7] is more sophisticated than Hurley's staging system and is likely to substitute it in clinical trials.[1] The authors suggest adding the HS Severity Index (HSSI),[3] a visual analog scale (VAS)[8] for pain, and using the Dermatology Life Quality Index (DLQI)[9] when assessing HS.[1] In the present study, we used the SS, HSSI, a VAS, and the DLQI. The inflammatory markers ESR and CRP were also measured. Normal ranges used in this study were 0–5 mg/dl for CRP and 0–15 mm/h for ESR. The final results of the DLQI were computed by adding subscores together to give a total ranging from 0 to 30. Sample scoring of the HSSI (range: 0–19) was as follows: mild (0–7); moderate (8–12); and severe (>13). Pain was evaluated using a VAS on which 0 indicated "no pain" and 10 indicated "unbearable pain".[8] Patients were evaluated before treatment (week 0), after the completion of the 20 sessions of HBOT (week 4, T4), and at the end of week 10 (T10).

Statistical analysis

Statistical analyses were performed using SPSS for Windows Version 16.0 (SPSS, Inc., Chicago, IL, USA). Quantitative data were tested for normal distribution using the Kolmogorov–Smirnov test. Data distribution was normal for all parameters except ESR (T4) in the HBOT group and CRP and HSSI (at T4 and T10, respectively) in the control group. The Wilcoxon signed rank test and the paired *t*-test were used to compare each group's pre- and post-treatment outcomes. The Mann–Whitney *U*-test and independent samples tests were used to test for statistically significant differences between groups. The chi-squared test was used to analyze treatment efficacies. Fisher's exact test was used instead of the chi-squared test when any expected frequency was <1 or when 20% of expected frequencies were ≤5. Results are expressed as the mean ± standard deviation (SD). A *P*-value of <0.05 was considered to indicate statistical significance.

Results

Forty-three patients (25 women, 18 men) were enrolled. The average age of the patients was 35.7 years (range: 20–55 years). Clinical and demographic data (mean age, sex, BMI, smoking, duration of disease, age of onset, and family history) for the patients are summarized in Table 1. Of the 43 patients, 32 had moderate HS and 11 had severe HS, as defined by the HSSI.

These 43 patients were randomly divided into two groups. In the first group, patients ($n = 22$) were treated with antibiotics and HBOT (HBOT group). In the second group, patients ($n = 21$) were treated with antibiotics only (control group).

The two groups did not differ in terms of gender distribution or smoking habits ($P > 0.05$, chi-squared tests). The groups were comparable with regard to age and BMI ($P > 0.05$, independent samples tests). The groups were also matched for DLQI, HSSI, SS, VAS, ESR, and CRP values before treatment ($P > 0.05$, independent samples tests). The groups showed a statistically significant difference in duration of disease (HBOT group, 7.09 ± 5.639 years; control group, 11.00 ± 4.648 years; $P < 0.05$, independent samples test).

Baseline data and treatment results at the end of weeks 4 and 10 (mean ± SD) and a comparison of means are presented in Table 2. Substantial improvement in the affected areas was observed (Fig. 1). We compared the proportions of patients with a decrease of ≥50% in symptoms (based on the SS, HSSI, DLQI and VAS scores) from baseline to weeks 4 and 10 in the two groups in order to

Table 1 Main clinical and demographic data for patients with hidradenitis suppurativa treated with antibiotics with and without hyperbaric oxygen therapy (HBOT)

	Antibiotic + HBOT (HBOT group, *n* = 22)			Antibiotic only (Control group, *n* = 21)			
	Female	Male	Total	Female	Male	Total	All patients
Patients, *n*	15	7	22	10	11	21	43
Age, years, mean	32.7	34.7	34.0	37.9	37.2	37.5	35.7
BMI, kg/m^2, mean	31.7	28.2	29.2	31.4	30.2	30.8	30.0
Current smokers, %	71.4	73.3	72.7	50.0	81.8	66.7	69.7
Cigarettes per day, mean	19.0	24.5	22.8	18.0	22.2	20.7	21.8
Age of onset, years, mean	27.0	26.1	26.6	27.4	26.7	27.1	26.9
Disease duration, years, mean	5.7	7.7	7.1	9.8	12.0	11.0	9.0
Family history	None	None	None	None	None	None	None

BMI, body mass index.

Table 2 Results of outcome parameters at weeks 0, 4 and 10 in patients with hidradenitis suppurativa treated with antibiotics with and without adjunctive hyperbaric oxygen therapy (HBOT)

	Week 0 Mean ± SD	Week 4 Mean ± SD	Week 10 Mean ± SD	*P*-value, weeks 0 vs. 4	*P*-value, weeks 0 vs. 10	*P*-value, weeks 4 vs. 10
Antibiotic + HBOT (HBOT group, *n* = 22)						
DLQI	18.27 ± 6.33	8.59 ± 5.77	5.50 ± 4.28	0.000	0.000	0.000
HSSI	12.73 ± 3.05	3.82 ± 1.82	2.50 ± 1.40	0.000	0.000	0.001
SS	17.06 ± 9.42	4.36 ± 3.45	3.50 ± 3.05	0.000	0.000	0.000
VAS	6.86 ± 0.88	2.17 ± 1.20	1.05 ± 1.09	0.002	0.065	0.010
ESR	24.68 ± 9.87	13.23 ± 9.48	8.36 ± 3.03	0.000	0.000	0.004
CRP	29.64 ± 38.96	5.09 ± 3.23	4.95 ± 3.21	0.001	0.002	0.547
Antibiotic only (control group, *n* = 21)						
DLQI	18.38 ± 6.46	11.38 ± 7.54	9.10 ± 7.54	0.000	0.001	0.000
HSSI	14.00 ± 3.19	6.52 ± 4.87	5.43 ± 5.27	0.000	0.000	0.001
SS	17.90 ± 9.54	8.61 ± 9.23	7.64 ± 9.33	0.000	0.000	0.000
VAS	6.67 ± 0.96	3.48 ± 2.15	2.48 ± 2.65	0.034	0.076	0.000
ESR	26.10 ± 10.47	16.9 ± 10.17	13.29 ± 8.67	0.000	0.000	0.003
CRP	31.81 ± 38.66	17.80 ± 30.85	14.00 ± 22.32	0.004	0.003	0.055

Calculated using the Wilcoxon signed rank test.
CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; ESR, erythrocyte sedimentation rate; HSSI, Hidradenitis Suppurativa Severity Index; SD, standard deviation; SS, Sartorius score; VAS, visual analog scale.

evaluate the adjuvant effect of HBOT. We also compared the proportions of patients whose test ESR and CRP values shifted from baseline into the normal range at weeks 4 and 10. In the control group, at week 10, these proportions amounted to 76.2, 71.4, 61.9, 71.4, 81.0, and 66.7% for SS, HSSI score, DLQI score, VAS score, ESR, and CRP level, respectively. In the HBOT group, great improvements from baseline were observed at week 10 in SS (100%), HSSI score (100%), DLQI score (95.5%), VAS score (100%), ESR (100%), and CRP level (72.7%). The results in the HBOT group were very encouraging. Treatment efficacies in the HBOT group were numerically better than in the control group ($P < 0.05$) (Table 3). By the end of weeks 4 and 10, statistically significant improvements were observed in HSSI score (T4 and T10, $P = 0.009$), SS (T4 and T10, $P = 0.021$), and DLQI score (T4, $P = 0.044$; T10, $P = 0.009$). By the end of week 10, statistically significant improvements were observed in VAS score ($P = 0.009$) and ESR ($P = 0.048$). Differences between data obtained at baseline and at the end of week 4 in VAS score ($P = 0.069$) and ESR ($P = 0.105$) were not statistically significant. No statistically significant improvements were observed in CRP from baseline to the end of weeks 4 ($P = 0.226$) and 10 ($P = 0.460$). All patients were asked about side effects during treatment. No adverse events were reported.

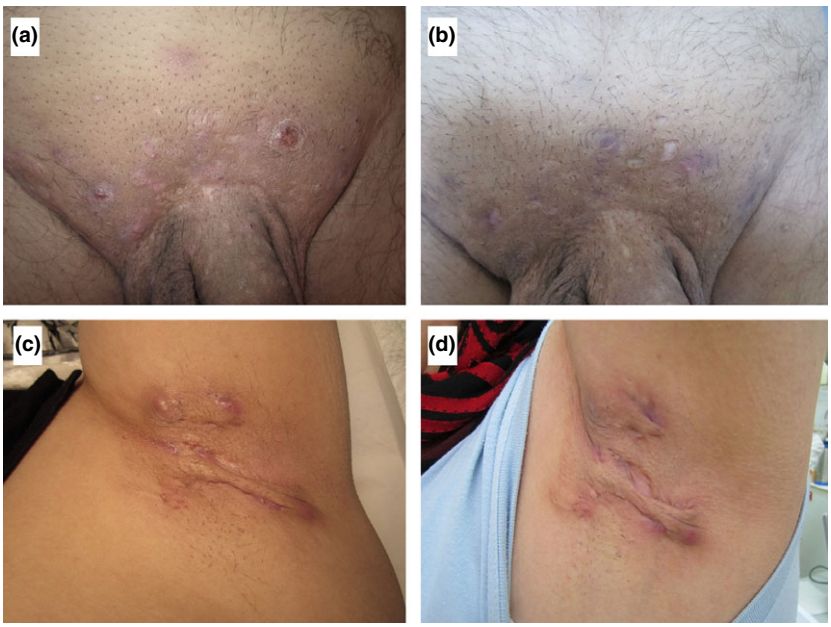

Figure 1 Clinical examination in patients with hidradenitis suppurativa (a, c) before and (b, d) after 4 weeks of antibiotic treatment with adjunctive hyperbaric oxygen therapy shows substantial improvement in the affected areas

Table 3 Proportions of patients with hidradenitis suppurativa treated with antibiotics with and without adjunctive hyperbaric oxygen therapy (HBOT) showing a ≥50% decrease in symptoms from baseline to weeks 4 and 10 in the study outcome parameters

	Patients with ≥50% decrease from baseline, %			Patients with ≥50% decrease from baseline, %		
	Week 4 Antibiotic + HBOT	Week 4 Antibiotic only	*P*-value	Week 10 Antibiotic + HBOT	Week 10 Antibiotic only	*P*-value
DLQI	77.3	47.6	0.044	95.5	61.9	0.009[a]
HSSI	100	71.4	0.009[a]	100	71.4	0.009[a]
SS	100	76.2	0.021[a]	100	76.2	0.021[a]
VAS	90.9	66.7	0.069[a]	100	71.4	0.009[a]
	Patients whose test value shifted to normal levels from baseline, %			Patients whose test value shifted to normal levels from baseline, %		
ESR	90.9	71.4	0.105[a]	100	81.0	0.048[a]
CRP	72.7	57.1	0.226[b]	72.7	66.7	0.460[b]

[a]Fisher's exact test.
[b]Chi-squared test.
DLQI, Dermatology Life Quality Index; HSSI, Hidradenitis Suppurativa Severity Index; SS, Sartorius score; VAS, visual analog scale.

Discussion

Hidradenitis suppurativa is a chronic, inflammatory disease of the apocrine glands. It is characterized by recurrent infections, abscess formation, and scarring.[1,4,10] The disease is more common in women than in men, and onset usually occurs during the mid-20s to early 30s.[2] Obesity and smoking both appear to increase the risk for HS, and up to 88.9% of affected individuals have been reported to be smokers.[1,4] Patients should be advised to lose weight, avoid tight-fitting clothing, and stop smoking.

Hidradenitis suppurativa is not primarily an infectious disease, although bacterial infection is often present.

However, bacteria are suspected of playing a role in the disease process, probably through immune-mediated mechanisms of inflammation.[11] The exact etiology of HS is unknown.[4] Previously, the efficacy of oral clindamycin and rifampicin treatment was shown to range from 71.4% to 85.7%.[4,5,11] The maximum effect of treatment appeared within 10 weeks.[4,5] In the present study, patients were treated with a combination of oral rifampicin 300 mg b.i.d. and clindamycin 300 mg b.i.d. for 10 weeks. When we analyzed the results (DLQI, HSSI, SS, VAS, ESR, and CRP) in both groups separately, statistically significant improvements were seen for each parameter (Table 2). We can conclude that the treatment of both groups was effective. These results were expected because patients in both groups underwent the same type of antibiotherapy. Successful antibiotherapy was seen in at least 75% of patients with stage 1 and 2 HS in previous studies,[4,5] and comparable results were obtained here.

Experimental research reports a possible HBOT-mediated enhancement of the activity of antibiotics through an additive intracellular effect.[12] The mechanism behind the positive effect of HBOT on HS when it is used in conjunction with the combination of oral rifampicin and clindamycin remains unknown. However, HBOT has been demonstrated to have the following effects.[12] Anti-infective properties of HBOT act in synergy with antibiotics. The treatment has a direct toxic effect on anaerobic bacteria. It improves leukocyte destruction of phagocytized bacteria and suppresses exotoxin production. It also improves wound healing by supporting fibroblast proliferation, collagen synthesis, angiogenesis, and epithelialization.[12] We suggest that HBOT can be used adjunctively to address the clinical issues of HS because oxygen, at increased pressures, augments tissue oxygen partial pressure, which facilitates increased bactericide by providing substrate for the formation of oxygen free radicals and augmenting the respiratory burst. During the healing process, hyperoxia causes increased formation of capillaries for oxygen, nutrient and antibiotic delivery, leading to an increased efficacy of some antibiotics in the high-oxygen environment, and possibly more rapid overall wound healing.[13]

Hyperbaric oxygen therapy has been successfully used alone or as an adjunctive measure to manage problem wounds, gas gangrene, necrotizing soft tissue infections, compromised skin grafts and flaps, refractory osteomyelitis, osteoradionecrosis, neurosurgical infections, and thermal burns.[6,14–16] In the present study, treatment efficacies in the HBOT group were numerically better than in the control group ($P < 0.05$) (Table 3). By the end of weeks 4 and 10, statistically significant improvements were observed in HSSI score (T4 and T10, $P = 0.009$), SS (T4 and T10, $P = 0.021$), and DLQI score (T4, $P = 0.044$; T10, $P = 0.009$). Adjunctive HBOT was considered effective in significantly improving the antibiotic treatment of HS. These results are important because the study showed that HBOT may increase the efficacy of antibiotherapy, reduce the time required to heal, and accelerate the patient's return to work, which will reduce the economic and social burden imposed by the disease. The study represents the first formal controlled clinical trial of adjunctive HBOT in the treatment of moderate to severe HS. Although the number of cases in this study was small, adjunctive HBOT was considered effective and to act synergistically with antibiotic treatment. Prospective randomized controlled trials including larger cohorts are required to confirm these results.

Conclusions

Adjunctive HBOT was considered effective and to significantly improve the efficacy of antibiotic treatment of HS. Hyperbaric oxygen therapy was well tolerated, and no unexpected safety issues were identified. This strategy may reduce the time required to heal and accelerate the patient's return to work, which reduces the economic and social burden of the disease.

References

1 Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. *J Am Acad Dermatol* 2009; **60**: 539–561.
2 Lee RA, Dommasch E, Treat J, *et al.* A prospective clinical trial of open-label etanercept for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol* 2009; **60**: 565–573.
3 Grant A, Gonzalez T, Montgomery MO, *et al.* Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol* 2010; **62**: 205–217.
4 Scheinfeld N. Hidradenitis suppurativa: a practical review of possible medical treatments based on over 350 hidradenitis patients. *Dermatol Online J* 2013; **19**: 1.
5 Gener G, Canoui-Potrine F, Revuz JE, *et al.* Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. *Dermatology* 2009; **219**: 148–154.
6 Uzun G, Ozdemir Y, Mutluoglu M, *et al.* Hyperbaric oxygen therapy as an adjunct to surgical treatment of extensive hidradenitis suppurativa. *World J Surg* 2010; **34**: 861–862.
7 Revuz J. Modifications to the Sartorius score and instructions for evaluating the severity of suppurativa hidradenitis. *Ann Dermatol* 2007; **134**: 173–174.
8 Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005; **14**: 798–804.

9 Acioz E, Gokdemir G, Koslu A. Quality of life in dermatology. *Turkderm* 2003; **37**: 16–23.
10 Prasad PV, Kaviarasan PK, Joseph JM, *et al.* Familial acne inversa with acne conglobata in three generations. *Indian J Dermatol Venereol Leprol* 2008; **74**: 283–285.
11 Bettoli V, Zauli S, Borghi A, *et al.* Oral clindamycin and rifampicin in the treatment of hidradenitis suppurativa-acne inversa: a prospective study on 23 patients. *J Eur Acad Dermatol Venereol* 2014; **28**: 125–126.
12 Mathieu D, ed. *Handbook on Hyperbaric Medicine*. New York, NY: Springer, 2006: 343.
13 Clark LA, Moon RE. Hyperbaric oxygen in the treatment of life-threatening soft-tissue infections. *Respir Care Clin N Am* 1999; **5**: 203–219.
14 Chen TL, Lin SL, Liu GQ, *et al.* Effects and holding time of hyperbaric oxygen on human severe periodontitis. *Shanghai Kou Qiang Yi Xue* 2003; **12**: 403–405.
15 Ma YH, Lei YH, Zhou M, *et al.* Effects of hyperbaric oxygen therapy in the management of chronic wounds and its correlation with $CD34^+$ endothelial progenitor cells. *Zhonghua Yi Xue Za Zhi* 2011; **91**: 3214–3218.
16 Pushkar Dlu, Zaitsev AV, Gavrilenko AP, *et al.* Hyperbaric oxygenation in combined treatment of interstitial cystitis. *Urologiia* 2010; **1**: 22–24 [In Russian].

