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ORIGINAL ARTICLE

Hyperbaric oxygen therapy does not improve the effects of standardized treatment in a severe attack of ulcerative colitis: a prospective randomized study

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Abstract

Background and aims. Complementary therapy options are needed in the treatment of active ulcerative colitis (UC). Hyperbaric oxygen therapy (HBOT) has been shown to have positive effects in experimental models of colitis and perianal Crohn's disease. ***Methods.*** In the present prospective randomized open-label study, HBOT in addition to conventional medical treatment was compared with conventional treatment alone. The primary objective in this study was improved clinical outcome evaluated by Mayo score, laboratory tests and fecal weight. The secondary objectives were improvement in health-related quality of life, avoidance of colectomy and evaluation of HBOT safety. ***Results.*** The authors found no statistically significant differences between the treatment groups in any of the assessed variables. ***Conclusion.*** The study results do not support the use of HBOT as a treatment option in a severe attack of UC.

Key Words: *complementary therapies, hyperbaric oxygenation/therapy, inflammatory bowel diseases, ulcerative colitis*

Introduction

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease (IBD) that causes chronic inflammation of the large bowel. The common clinical manifestations of UC are frequent and sometimes bloody diarrhea, abdominal pain and general discomfort, which may have a significant impact on patients' health-related quality of life (HRQoL) [1,2].

The IBD pathogenesis is probably associated with continuous antigenic stimulation by agents such as commensal enteric bacteria, fungi or viruses. In genetically susceptible individuals, this leads to chronic intestinal inflammation, possibly due to defects in the mucosal barrier function, microbial killing or immunoregulation [3–6]. Some alternative mechanisms may be of importance for the initiation, maintenance and deterioration of UC; the suggested pathogenetic factors include endothelial dysfunction, thromboembolic formation in the capillary bed and microcirculatory changes causing mucosal hypoxia resulting in mucosal damage and decreased healing capacity [7–9].

Traditionally, severe attacks of UC require intensive glucocorticosteroid (GCS) treatment. At present, most non-responders or weak responders to GCS are offered "rescue medical treatment" mainly with tumor necrosis factor-α inhibitor or calcineurin inhibitor [10]. Despite these medical efforts, a substantial number of patients still need a prompt colectomy [11].

Hyperbaric oxygen therapy (HBOT) is the established treatment for decompression sickness, arterial gas embolism and late radiation injury [12,13]. It has also been used to promote tissue healing in various clinical settings including the management of diabetic

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Table I. A summary of publications on HBOT in UC.

Author	Study design	Number of patients participating/ improved	HBOT parameters ATM; treatment time (min); total number of sessions	Side effects	Comments; outcomes
Buchman et al. [20]	Case report	1/1	2.0; 120; 30	Not reported	Pancolitis refractory to therapy (GCS, mercaptopurine, 5-ASA and antibiotics); clinical remission (effect lasted 2 months)
Demirturk et al. [21]	Case series	2/2	2.0; 120; 30	None	Pancolitis refractory to therapy (GCS, 5-ASA and total parenteral nutrition); clinical improvement after 2–3 weeks
Gurbuz et al. [22]	Case report	1/1	2.0; 120; 35	Not reported	Left-sided UC refractory to therapy (GCS, 5-ASA and AZA); remission (6 months reported)
Karkumov et al. [23]	Case series	34/34	Not defined; 60–75; 10–12	Not reported	Chronic UC; all patients improved after first 5–6 therapy sessions
Kuroki et al. [24]	Case report	1/1	2; 60; 27	None	UC with toxic megacolon, refractory to therapy (i.v. GCS and antibiotics); clinical improvement after 3 therapy sessions

Abbreviations: 5-ASA = 5-aminosalicylic acid; AZA = azathioprine; GCS = glucocorticosteroid; HBOT = hyperbaric oxygen therapy; UC = ulcerative colitis.

and vascular leg ulcers [14]. Beneficial effects have been described in patients with severe or refractory perianal Crohn's disease [15–18] and HBOT has also been found to be effective in decreasing tissue damage in models of experimental colitis [19].

A search of Medline and PubMed did not reveal any prospective randomized trials using HBOT in UC. The clinical outcome of HBOT in such patients has only been published in a few case reports of refractory cases and one series without a control group (Table I). All these reports indicate that HBOT may be a useful therapeutic option in UC. The authors have not been able to find any reports presenting absence of or negative effects of HBOT in UC.

The use of HBOT involves administration of 100% oxygen in a hyperbaric chamber at pressures two to three times greater than atmospheric. Although the exact biological mechanisms are not established, it has been postulated that decreased activity of nitric oxide synthase and inhibition of pro-inflammatory cytokines may be of importance for an anti-inflammatory effect [25,26]. In peripheral tissues, oxygenation is mainly dependent on the local circulation and the passive oxygen diffusion capacity. Tissue oxygen pressure is the result of the equilibrium between the amount of oxygen extracted by the tissue and the amount of oxygen consumed by the cells, defined by Fick's first law. Hence, when a hypoperfusion situation is present, the oxygen utilization in the cell can be critically low. The effect of HBOT on oxygen availability in the peripheral tissues is achieved via a high concentration of free oxygen molecules dissolved in plasma instead of bound to the circulating erythrocytes causing a substantial cellular oxygen availability [27]. HBOT is considered a safe method with few side effects when the used pressure does not exceed 2.8 atmospheres (ATM) and treatment sessions not exceeding 90 min. The most commonly reported adverse effects of HBOT are reversible myopia, middle ear barotrauma, psychological intolerance, pain from cranial sinuses and teeth and general seizures [14,16,18,28].

The present work investigated the effect of HBOT as an additional therapy in UC. The authors conducted a prospective randomized open-label interventional study on patients displaying severe attacks of newly diagnosed UC, or serious attacks of previously diagnosed UC.

The primary objective in this study was improved clinical outcome evaluated by Mayo score, laboratory tests and fecal weight. The secondary objectives were improvement in HRQoL, avoidance of colectomy and evaluation of HBOT safety.

Methods

Study design

The study design was prospective, randomized, open-labeled and interventional. Participants were randomized into one of two study groups using a web-based randomizing form (www.randomizer.org).

The control group (non-HBOT) was given the standard routine of intensive UC treatment with initial intravenous GCS treatment (betamethasone

4+0+4 mg (prednisolone equivalence 67 mg)), oral mesalazine (1 200 mg twice daily on days 1–5 and thereafter 2 400 mg twice daily), suppository prednisolone (20 mg once daily) and enema prednisolone (37.5 mg once daily). Patients allocated to the intervention group (HBOT) were given the same treatment with the addition of HBOT administered at 2.4 ATM for 90 min/session, 5 days/week, for 6 consecutive weeks (a total of 30 HBOT sessions). The protocol used for HBOT was the standard one applied for other diagnoses. Patients who attained a reduction of ≥3 in the Mayo score compared with baseline were classified as clinical responders, and were switched to a scheduled 7 weeks of prednisolone 40 mg once-daily tapering.

The study protocol was approved by the Ethics Committee of the University of Gothenburg (Dnr 492–07).

Objectives

The primary objective in this study was improved clinical outcome evaluated with Mayo score, laboratory tests and fecal weight.

The secondary objectives were improvement in HRQoL, avoidance of colectomy and evaluation of HBOT safety.

Patients

Eligible patients were those admitted to Sahlgrenska University Hospital/Östra Hospital with previously diagnosed UC or newly debuted clinical signs of UC according to clinical routine criteria. On admission, all patients showed clinical characteristics (frequent bloody diarrhea, abdominal pain and general discomfort) supported by abnormal peripheral blood tests.

The inclusion criteria were men and women aged above 17 years with a severe attack (Mayo score >10) of extensive or left-sided UC and negative fecal cultures (including *Clostridium difficile* toxin).

The exclusion criteria were presence of radiological signs of threatening colonic perforation, ongoing or planned pregnancy, symptomatic cardiovascular or pulmonary disease, previous bleomycin treatment within 2 months, epilepsy, dysfunction of tuba auditiva, psychiatric disease (claustrophobia, anxiety or psychotic disorders, drug or alcohol abuse) or ongoing systemic anti-inflammatory drugs (GCS, immunomodulators or tumor necrosis factor-α inhibitors). In case of previously diagnosed UC, 5-aminosalicylic acid (5-ASA) intake was allowed.

At inclusion, all patients underwent colonoscopy (preparation procedure: Klyx®, 120 ml × 2) with biopsy sampling in order to ensure the diagnosis visually as well as histologically and to define the inflammatory extent. A second colonoscopy was performed at the end of the study (day 180, preparation Laxabon®, 4 l) or at withdrawal from the study, in order to correlate endoscopic findings with the clinical outcome.

In order to assess the disease course and support the defined protocol management during the hospital stay, the authors constructed a Patients' Medical Safety Score (PMSS). However, the PMSS has not previously been validated. At baseline Mayo score, serum C-reactive protein (S-CRP), blood platelet count (B-TPK), blood erythrocyte sedimentation rate (B-ESR) and fecal calprotectin were registered. On day 3, PMSS was calculated by addition of one point each if an increase was registered in Mayo score (≥1 point), S-CRP (>10 mg/l) and B-TPK (>25%) compared with baseline values. On day 5, B-ESR was incorporated into the PMSS and added 1 point to the score if an increase of >5 mm/h was evident. On day 7, fecal calprotectin was added, with 1 point scored if there was an increase of more than 25% compared with baseline. The decisions based on the PMSS were the same for all assessments (i.e., on days 3, 5 and 7). A change in PMSS of 0–1 points (compared with baseline) resulted in continued treatment according to the study protocol. A score of 2 points led to a temporary doubling of the initial dosage of GCS. A level of 3 points, or an overall general clinical deterioration, resulted in a mandatory withdrawal from the study. In case of deterioration or lack of any clinical improvement (treatment failure) after day 7, the patients were withdrawn based on an overall clinical evaluation supported by PMSS impairment.

The length of the hospital stay was not predefined but varied depending on each patient's state, based on daily clinical examination and blood tests according to the protocol. The range of hospital stay was 3–30 days (median 7 days).

All responding patients left the hospital in a stable clinical condition. The patients were clinically followed according to the protocol at the authors' outpatient clinic for the study period of 180 days. Beyond 180 days, only the colectomy rate was registered. The first inclusion was performed in January 2008. The cohort was observed until 31 December 2012.

Registration of variables

All measurement occasions of blood/fecal samples and assessments of Mayo score are presented in Table II. The patients registered the daily fecal weight during their hospital stay.

Table II. Time schedule for the analyzed parameters: peripheral blood tests, urinary test, fecal samples.

	1	3	5	7	14	45	90	180
Fecal cultivation, U-HCG (women)	x							
B-Hemoglobin, B-TPK, S-CRP, Mayo score	x	x	x	x	x	x	x	x
S-AST, S-ALT, S-Alb, S-creatinine, S-electrophoresis	x			x		x	x	x
B-ESR	x		x	x	x	x	x	x
Fecal calprotectin	x			x				x

Abbreviations: B-TPK = blood platelet count; HRQoL = health-related quality of life; PMSS = Patients' Medical Safety Score; S-AST = serum-aspartate transaminase; S-ALT = serum-alanine transaminase; S-alb = serum-albumin; S-CRP: serum C-reactive protein; U-HCG = urine-human chorion gonadotropin.

With reference to the secondary objectives, HRQoL forms were registered repeatedly during the study period. Two questionnaires were used: the Short-Form-36 (SF-36) and the inflammatory bowel disease questionnaire (IBDQ). SF-36 is a well-validated questionnaire for measurement of general HRQoL [29]. The SF-36 results were presented in accordance with the SF-36 measurement model, as physical component summary (PCS) and mental component summary (MCS). The IBDQ is the standard instrument for assessment of HRQoL in adult patients with IBD. It consists of 32 items, each responding to a 7-point scale where 1 represents the worst condition and 7 represents the best condition. The items are grouped into four domains: bowel symptoms (B, range 10–70), systemic symptoms (S, range 5–35), emotional function (E, range 12–84) and social function (SF, range 5–35) [30].

All peripheral blood tests and fecal samples were analyzed at the central laboratory facility at Sahlgrenska University Hospital (ISO 15189).

Hyperbaric oxygen treatment chamber

The HBOT was performed in a multiplace hyperbaric chamber (manufactured by GDA Sverige AB, Göteborg, Sweden; serial number: 220098214; register number: s104189).

Statistics

The study planning calculation was based on the hypothesis that Mayo score, inflammatory parameters and fecal calprotectin are sensitive markers of clinical response to addition of HBOT. In the pre-study statistical calculation a 15% reduction of each mentioned variable was assumed with a 0.05 significance level and 90% power. Based on this assumption, the sample size was calculated to 2 times 12 patients. An interim analysis, evaluating achievement of expected treatment effects and safety, was planned when at least half of the study population had completed (per protocol) the treatment period. The interim

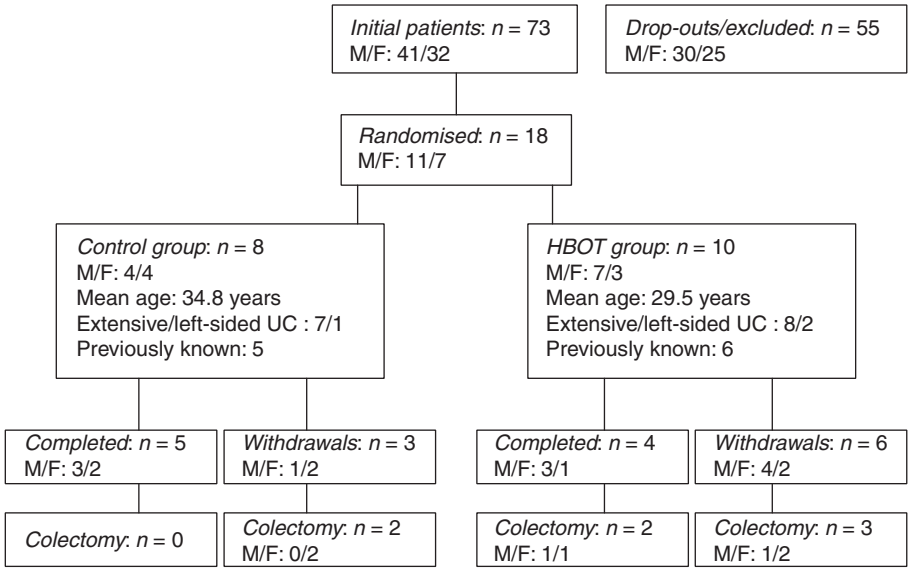

Figure 1. Flow chart illustrating the study progress, patient characteristics and colectomy rate (M/F: male/female).

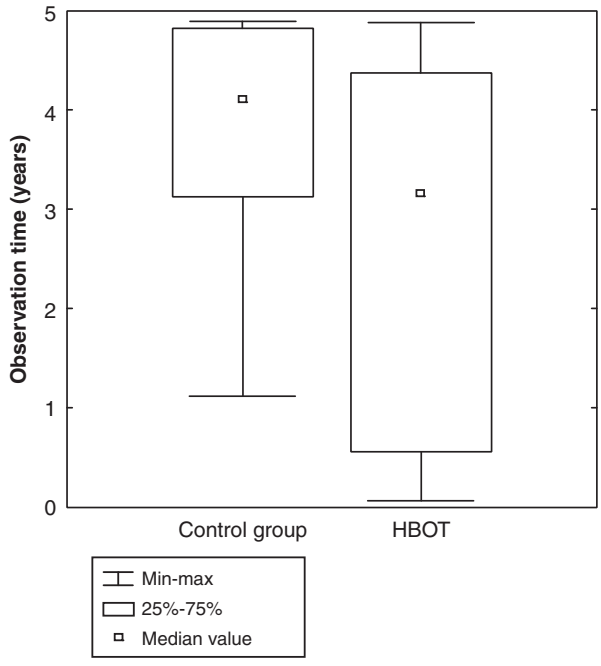

Figure 2. SF-36 results at baseline and on day 180.

analysis was not taken into account in the pre-study statistical calculation. A two-sided Fisher's permutation test (intention-to-treat analysis) was used throughout the study at the 0.05 significance level.

Results

During the inclusion period, 73 patients were considered for the screening procedure and were given oral and written information about the study, and signed the consent form. The distribution of the patients into the treatment groups is shown in Figure 1. The UC diagnosis was verified by macroscopic and histological evaluation of the colonoscopy in each participant. A total of 36 patients did not meet the inclusion criteria and were therefore excluded from the study (Figure 1). A further 19 declined participation, mainly due to the limitation of normal daily activities that would be necessary given the considerable time consumption associated with the HBOT. No patients were excluded from entering the study due to threatening acute complications on admission to the hospital. The pre-study statistical calculation stated that 24 patients should have been included in the study. The conducted interim analysis (performed when 12 patients had passed day 180 in the study) showed that the differences in HBOT effects were too small to reach any statistical differences between the study groups even if the planned number of patients would have completed the study. Following the interim analysis an additional statistical calculation was performed, showing that a considerable expansion, i.e. a four times expansion, of the participants would have been necessary in order to detect a possible difference. Finally, the final study group consisted of 18 patients. Nine patients (six receiving HBOT and three with conventional treatment only) were withdrawn prematurely from the study between days 1 and 46. Of these, two patients were classified as early dropouts, one because of perceived claustrophobia during the first session of HBOT, and another because of an inability to normalize the middle ear pressure, which became obvious after two sessions of HBOT. The remaining seven withdrawals were due to worsening of the clinical state, which was also reflected by impairment of the PMSS.

The observation time for both groups is presented in Figure 2. The results showed no significant differences in the primary objectives concerning clinical improvement in terms of either Mayo score (median value 11 at inclusion in both groups, median value 3 in control group and median value 0.5 in HBOT group at day 180), peripheral laboratory tests or faecal calprotectin (data not shown). Fecal weight was registered during the hospital stay for a maximum of 10 days. The results from day 1 and 5 are illustrated in Figure 3. No significant differences were found between the two treatment groups.

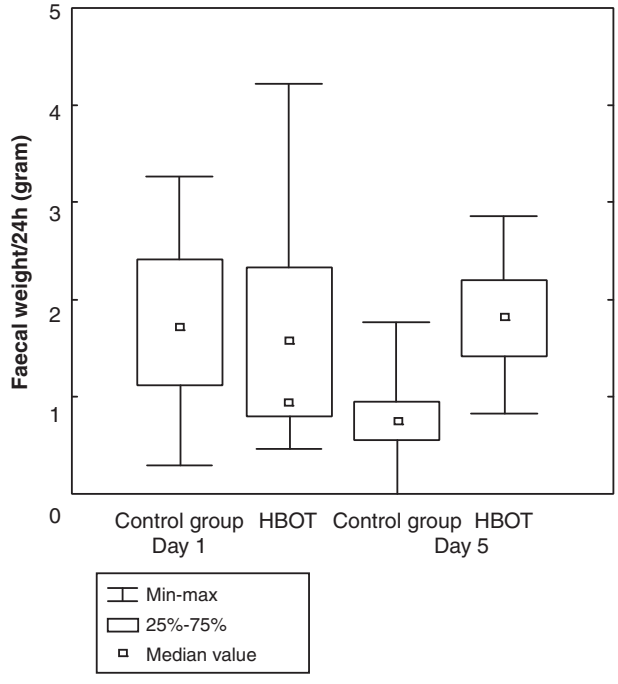

Figure 3. Box plot illustration of the faecal weights in both patent groups on day 1 and 5.

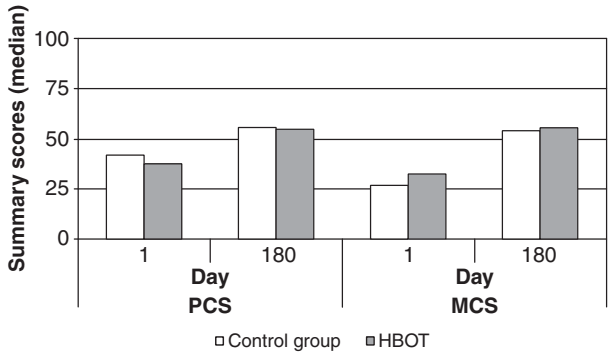

Figure 4. SF-36 results (median values) at baseline and on day 180. The results are presented in accordance with the SF-36 measurement model, as physical component summary (PCS) and mental component summary (MCS).

No detectable differences regarding HRQoL were registered during the study period and data from day 1 and 180 are presented. SF-36 results are presented in Figure 4 as PCS and MCS. There were no significant differences between the two patient groups. IBDQ also showed no significant differences between the groups (Table III).

Seven patients (five in the HBOT group and two in the control group) underwent colectomy (Figure 1), in two cases due to a severe medical deterioration during the hospital stay. Otherwise, no unexpected adverse events of HBOT were observed in this study.

Discussion

Complementary therapy options are needed in active UC in order to improve the clinical outcome of the disease, both in general and for severe attacks in particular. In this study, conventional treatment was compared with addition of HBOT. The motivation for this prospective randomized study was the existence of a small number of encouraging individual case reports describing positive effects of HBOT in the treatment of refractory UC. The validity and clinical applicability of these case reports are limited, and to date there has been only one published article (in Bulgarian) with a sufficient number of patients reporting a positive outcome of HBOT in UC [26]. In addition, the results of that study are difficult to interpret in the absence of a control group and given the lack of careful description of either patient characteristics such as disease severity or the inclusion and exclusion criteria.

The primary objective in the present study was to achieve an improved clinical outcome for patients with a severe attack of UC. The secondary objectives were improved HRQoL, reduced colectomy rate and to demonstrate the safety of HBOT.

Table III. IBDQ results (median values) at baseline and on day 180 grouped into four domains: bowel symptoms (B, range 10–70), systemic symptoms (S, range 5–35), emotional function (E, range 12–84) and social function (SF, range 5–35).

		IBDQ	
		Day	
	Domains	**1**	**180**
Control	B	35.5	65
HBOT		*33.5*	*60.5*
Control	S	15	33
HBOT		*12*	*32*
Control	E	47	80
HBOT		*43*	*75.5*
Control	SF	15	35
HBOT		*14*	*35*

Abbreviations: HBOT = hyperbaric oxygen therapy; IBDQ = inflammatory bowel disease questionnaire.

The results revealed none of the proposed positive effects on clinical outcome evaluated with Mayo score, laboratory tests, fecal weights, HRQoL forms and reduced colectomy rate.

The authors identified some shortcomings in our study. The main limitation was the small number of patients captured for enrolment due to the early study closure as a result of the pre-study planned interim analysis. This analysis was conducted in order to assess the effect and safety of further inclusion. The analysis showed no positive results with respect to the objectives, thereby indicating that continuation of the study would not reach any significant positive outcome of importance. With regard to the interim analysis, the authors realized that a completion of the number of planned participants or a small enlargement of the material would not yield significant results in any of the assessed variables. In consequence, the authors then closed further enrolment which also was reinforced by the significant impact on daily activities for each patient.

A possible confounding factor may be the open-label design. It could have been theoretically possible to arrange a single blinded study design by creating a placebo situation for the control group in the hyperbaric chamber. This could have been achieved through reduction of the oxygen concentration in the breathing gas at 2.4 ATM, which would have led to an unchanged tissue–gas exchange state in accordance with postulated gas laws. However, this arrangement was not feasible since the current situation already required some disruption to the scheduled clinical use of the pressure chamber, and additional separate therapy sessions were not a realistic scenario.

A third possible weakness is that the regimen of HBOT was adopted from HBOT use in other clinical

situations. Thus, the possibility that a different HBOT protocol might have a positive clinical effect in UC cannot be excluded.

Finally, the patients in this study constituted a group with a defined severe stage of acute UC with known high risk of intractable inflammatory condition *per se* resulting in a poor prognosis. As per the authors' knowledge, HBOT has not been tested in clinical UC studies in patients with moderate or retractable UC in any protocol.

The observed increase in number of colectomies in the HBOT group is a non-significant tendency that could be a conceivable disadvantage of HBOT in a severe attack of UC. The apparent difference cannot be explained by differences in disease activity at baseline or by differences in medical treatment during the study.

In conclusion, neither the primary nor the secondary objectives were achieved in this study. Fully aware of the limitations mentioned above, particularly the small numbers of participants, the study results do not support the use of HBOT as a treatment option in a severe attack of UC.

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