Safety and Efficacy of Hyperbaric Oxygen Therapy for the Treatment of Interstitial Cystitis: A Randomized, Sham Controlled, Double-Blind Trial

Arndt van Ophoven,* Gordon Rossbach, Frank Pajonk and Lothar Hertle

From the Department of Urology, Universitätsklinikum Münster and Center for Hyperbaric Medicine (GR), Münster, Germany, and Department of Radiation Oncology, David Geffen School of Medicine at UCLA, Los Angeles, California (FP)

Purpose: We conducted a double-blind, sham controlled study to evaluate the safety, efficacy and feasibility of hyperbaric oxygenation for interstitial cystitis.

Materials and Methods: A total of 21 patients with interstitial cystitis were randomized to 90 minutes treatment in a hyperbaric chamber pressurized with 100% O_2 to 2.4 atmosphere absolute for 30 treatments sessions or 1.3 atmosphere absolute, breathing normal air in the control group. Moderate or marked improvement in a global response assessment questionnaire was defined as treatment response (primary outcomes). Secondary measurements included changes of pain and urgency evaluated by visual analog scales, functional bladder capacity and frequency. Changes in the O'Leary-Sant Interstitial Cystitis Index and rating of overall satisfaction with the therapeutic outcome were also reported.

Results: There were 3 of 14 patients on verum and no control patients who were identified as responders ($p < 0.05$). At 12-month followup 3 patients (21.4%) still reported treatment response. Hyperbaric oxygenation resulted in a decrease of baseline urgency intensity from 60.2 ± 15.0 to 49.9 ± 35.2 mm at 3 months and decrease of pain intensity from 43.1 ± 20.5 to 31.2 ± 19.8 mm, respectively ($p < 0.05$). The Interstitial Cystitis Symptom Index score sum decreased from 25.7 to 19.9 points in patients on verum. Sham treatment did not result in improvement of the baseline parameters.

Conclusions: A total of 30 treatment sessions of hyperbaric oxygenation appear to be a safe, effective and feasible therapeutic approach to interstitial cystitis. In the treatment responders application of hyperbaric oxygenation resulted in a sustained decrease of interstitial cystitis symptoms with a discordant profile regarding the peak amelioration of the various interstitial cystitis symptoms compared with a normobaric, normoxic sham treatment.

Key Words: cystitis, interstitial; pelvic pain; hyperbaric oxygenation; clinical trials

In a recent observational study we reported the therapeutic potential of HBO for IC.[1] We then conducted a randomized, double-blind, sham controlled study, serving as proof of principle, to further assess the safety and efficacy of HBO as a novel therapeutic approach to IC.

PATIENTS AND METHODS

The study comprised 21 patients 18 years old or older who met the diagnostic criteria of the National Institute of Diabetes and Digestive and Kidney Diseases for IC. The protocol was approved by the local ethical review board and written informed consent was obtained from all patients. The HBO treatment schedule contained 30 treatment sessions of 100% oxygen inhalation via a facial mask at a chamber pressure of 2.4 ata in a multiplace hyperbaric chamber. Treatment was given in daily sessions, 6 times a week during a treatment period of 5 weeks. Oxygen was inhaled for 90 minutes, and each treatment session lasted approximately 120 to 135 minutes including compression and decompression times. The sham treatment was conducted identically to the described verum sessions except that the patients breathed normal air instead of 100% oxygen via a facial mask at a faintly increased pressure of 1.3 to 1.4 ata, to simulate compression and its effects on the tympanum (normobaric, normoxic sham treatment). All patients and investigators, except the operators of the hyperbaric chamber and the trial statistician, were blind to treatment assignments. Verum treatment free of charge was offered to all potential control patients during recruitment and was performed after unblinding.

Patients were randomly allocated to sham or verum treatment following a 1:2 distribution to increase acceptance of and adherence to the study protocol. The code was broken after evaluation at 3 months. Followup was continued in treatment responders for 12 months. In patients reporting no evidence of efficacy the followup was terminated after unblinding.

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* Correspondence: Klinik und Poliklinik für Urologie, Universitätsklinikum Münster, Albert Schweitzer-Str. 33, 48129 Münster, Germany (telephone: ++-49-251-8347466; FAX: ++-49-251-8345279; e-mail: avo@uni-muenster.de).

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TABLE 1. *Response to HBO with regard to self-administered GRA*

	3 Mos		6 Mos	9 Mos	12 Mos
	V	SC	V	V	V
No. pts	14*	7	12	12	12
GRA category:					
Markedly worse	—	—	—	—	—
Moderately worse	—	—	1†	—	—
Slightly worse	—	4	—	—	—
No change	5	3	5	7	7
Slightly improved	6	—	2	2	2
Moderately improved	2	—	3	2	2
Markedly improved	1	—	1	1	1
No. of responders	3‡	0	4	3	3

* Including 2 dropouts for intent to treat analysis.
† Bacterial cystitis at followup appointment.
‡ $p < 0.05$.

The efficacy of HBO treatment was assessed at the end of treatment and after followup intervals of 1, 3, 6, 9 and 12 months. Alteration in patient assessment of overall change in condition (GRA) served as the primary outcome measurement. The GRA is a 7-point centered scale rating overall well-being, and includes markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved and markedly improved. Patients who reported any of the latter 2 categories were defined as treatment responders. Secondary outcome parameters were changes in pain and urgency from baseline using VAS. Further secondary measures of efficacy addressed changes in urinary frequency and functional bladder capacity (48-hour voiding log). An additional outcome measure was a change from baseline in the ICSI. This validated, self-administered index comprises 8 questions assessing pain and voiding symptoms. The maximum index score sum of 36 reflects maximum symptom and problem severity and the lowest possible score sum is 0.[2] Finally, patients were requested to rate their satisfaction with the therapeutic outcome as poor, fair, good or excellent.

Concurrent therapy for IC was discouraged during the study period, but patients were basically allowed to stay on their baseline IC medication and had to anticipate continuing their medication at the same stable dose throughout the study. However, patients who requested additional therapeutic options during the study were considered nonresponders and were included in the denominator of response rates. Reasonable efforts were made to actively determine all prescription and nonprescription medications taken by the patients before and during the study. All relevant information was recorded in the case report forms.

Changes in all of these parameters were evaluated in responders after unblinding at the aforementioned followup appointments, to assess sustained effects of HBO treatment. Secondary to being a pilot study, an initial sample size calculation was not performed. The appropriate patient number was determined as much by the feasibility of testing a complex and time-consuming treatment as by statistical considerations. A sample size of 21 was judged to feasibly provide some indication of whether HBO has any effect on IC symptoms. Primary and secondary efficacy analyses were based on randomized 2:1 treatment assignment for all patients who received treatment and had at least 1 evaluable post-baseline observation (intent to treat). Baseline factors were compared among groups using Fisher's exact and Mann-Whitney U tests. Statistical comparisons were made using the Mann-Whitney U test for changes in the outcomes parameters, ie symptom score, changes in pain and urgency intensity, and changes in voiding patterns (frequency, functional bladder volume). Chi-square statistics were calculated to compare proportion of responders among groups, with $p < 0.05$ considered significant at 80% power. All statistical tests were 2-tailed, and calculations were performed using SPSS® and SAS® statistical software packages.[3]

RESULTS

Between October 2003 and June 2004 a total of 21 female patients with a mean age of 65.5 ± 8.8 years (range 42.2 to 78.0) were enrolled in the study. There were 7 patients (mean age 68.4 ± 5.2 years) who received sham treatment and 14 (mean age 62.5 ± 10.9 years) who received verum treatment. Two patients who received verum treatment dropped out of the study. One woman presented clinical signs of a mild oxygen intoxication, the second patient dropped out due to poor adherence to treatment protocol (repeated absence at treatment appointments).

After unblinding 3 of 14 patients in the treatment arm and none of the patients in the sham treatment arm were identified as responders ($p < 0.05$, table 1). At 12 months followup 3 patients (21.4%) still reported response to HBO treatment. Table 2 lists patient numbers regarding satisfaction with the therapeutic outcome and reveals that at 6-month followup 5 patients reported either good or excellent satisfaction with their therapeutic results and 3 patients at 12 months respectively. One woman, reporting an excellent satisfaction with HBO therapy, experienced this grade of therapeutic contentment throughout followup.

Regarding further secondary outcome parameters, table 3 shows the baseline clinical data and symptom changes of the 21 patients during the blinded part of the trial. Sham treatment did not result in improvement of any baseline parameter. Pain intensity increased from 51.4 at baseline to 55.7 mm at 3 months with sham treatment. Verum treatment resulted in a decrease of urgency intensity from 60.2 at baseline to 49.9 mm at 3 months with a peak efficacy at end of treatment (47.9 mm, ie a 24% decrease of urgency intensity). Even more impressively a decrease of pain intensity from 43.1 to 29.0 mm was observed at 3 months in patients on verum, ie a decrease of 28% in pain intensity ($p < 0.05$). The ICSI score sum decreased from 25.7 to 19.9 points in the patients on verum, however urinary frequency and functional bladder volume remained more or less stable during the first 3 months of followup.

TABLE 2. *Patient numbers regarding satisfaction with the therapeutic outcome of HBO at followup appointments*

	3 Mos		6 Mos	9 Mos	12 Mos
	V	SC	V	V	V
No. pts	14*	7	12	12	12
Satisfaction:					
Poor	5	7	5	7	7
Fair	4	0	2	2	2
Good	4	0	4	2	2
Excellent	1	0	1	1	1

* Including 2 dropouts for intent to treat analysis.

TABLE 3. *Changes in symptoms from baseline to 1 and 3-month followup comparing 14 patients on verum with 7 patients on placebo*

	Mean ± SD			
	Baseline	End of Treatment	1 Mo Followup	3 Mos Followup
ICSI score sum:				
V	25.7 ± 5.7	21.9 ± 7.1	20.6 ± 7.8	19.9 ± 7.9
SC	27.3 ± 3.9	26.6 ± 4.9	26.5 ± 5.5	26.7 ± 5.8
Pain (mm on VAS):				
V	43.1 ± 20.5	37.1 ± 23.9	33.9 ± 22.1	31.2 ± 19.8*
SC	51.4 ± 24.1	51.9 ± 27.2	52.1 ± 22.7	55.7 ± 27.8
Urgency (mm on VAS):				
V	60.2 ± 15.0	47.9 ± 19.0	48.6 ± 23.4	49.9 ± 35.2
SC	64.3 ± 23.0	65.0 ± 28.2	64.8 ± 24.5	65.0 ± 25.7
24-Hr frequency:				
V	16.2 ± 5.1	17.5 ± 6.1	17.5 ± 6.3	15.9 ± 7.0
SC	18.9 ± 4.3	19.0 ± 4.5	19.5 ± 5.9	20.9 ± 6.5
Bladder vol (ml):				
V	127 ± 55	137 ± 69	139 ± 61	147 ± 49
SC	119 ± 48	120 ± 35	117 ± 52	118 ± 36

For the 2 dropouts the latest evaluable post-baseline observation was analyzed.
* $p < 0.05$ for difference between verum and sham outcome compared with baseline.

Table 4 shows the changes in symptoms regarding the 3 responders throughout the study. Maximum pain amelioration was reached at 3 months in 2 of the 3 responders. Regarding amelioration of urgency the clinical course of the responders showed a peak efficacy from 6 to 9 months in 2 of the 3 responders. Changes in functional bladder volume set in at 3 months lasting throughout remaining followup.

Of the 7 control patients 5 decided to undergo open label HBO treatment after unblinding. There were 2 patients who reported moderate improvement of their well-being on the GRA throughout a followup interval of 12 months. Satisfaction with the therapeutic outcome was rated good throughout the followup based on amelioration of various symptoms. Pain decreased from a baseline intensity of 50 mm and 20 mm to a peak amelioration of 30 mm and 5 mm. Urgency decreased from 60 mm and 40 mm to 35 mm and 15 mm, respectively. The 24-hour frequency decreased from 19.5 and 20.5 baseline voids to a minimum of 8.5 and 15.5 voids and functional bladder volume increased from 164 ml and 64 ml to a maximum of 209 and 145 ml, respectively.

Four patients in the treatment arm reported transient problems with accommodation during treatment that were not further reported at 3-month followup. One woman reported mild eustachian tube dysfunction during treatment sessions, resulting in a transient hearing impairment within the chamber. The events were solved by intense chewing of some candy or gum, resulting in the opening of the tube with subsequent pressure balance between the middle ear and the environment. A decongesting nasal spray was occasionally administered some minutes before start of and/or during treatment. Oral medication was given to control temporary claustrophobia in another patient at the start of the study.

DISCUSSION

This randomized controlled study generated clinical evidence to support previous findings that HBO ameliorates symptoms of IC. The biological effect of HBO has been extensively explained elsewhere, in summary HBO aims at ischemia by leading to a net gain in oxygen concentration in tissues.[1] The hyperbaric chamber provides unique conditions in which the hemoglobin is fully saturated and the oxygen is dissolved in the blood plasma at the rate of 2.3 volume percentage of hyperoxemia per 1 ata. This amount of hyperoxygenation cannot be achieved by any other means available in medical practice. These high doses of oxygen promote physiological mechanisms that have clinical effects in different pathological ischemic conditions, eg impaired oxygen delivery or impaired oxygen metabolism.[4] Ischemia of the bladder wall has been reported in IC. In a previous study Rosamilia et al demonstrated a decreased overall density of vessels in the subepithelium of bladder biopsies obtained from women with IC.[5] In accordance with these data Irwin et al reported that bladder perfusion is impaired in IC bladders, especially during the filling phase, using laser Doppler measurements.[6] Pontari et al also noted that bladder perfusion was decreased during bladder filling in IC cases but increased in control cases.[7] Another painful condition induced by hypoxemic processes is sympathetic reflex dystrophy, also referred to as CRPS.[8] Based on several pathophysiological and clinical parallels between both con-

TABLE 4. *Changes of symptoms in 3 treatment responders*

	ICSI Score Sum	Pain (mm on VAS)	Urgency (mm on VAS)	24-Hr Frequency	Bladder Vol (ml)
Baseline	19/26/24	30/40/50	30/80/60	13/20/11	118/84/165
End of treatment	6/19/15	5/20/10	15/40/20	10/13/10	159/100/180
Mos followup:					
1	12/21/9	50/20/10	10/40/15	11/13/8	142/117/200
3	12/20/6	20/10/0	20/40/10	12/13/8	179/124/220
6	21/19/6	40/20/0	35/35/5	16/13/8	120/156/220
9	14/8/6	20/40/0	20/35/5	12/13/8	176/126/220
12	15/19/6	25/40/0	25/40/5	12/13/8	180/140/220

Position of actual number, separated from others by slash, continually refers to the same patient.

ditions, IC has previously been discussed to represent a CRPS of the pelvic organs, especially the bladder.[9,10] Notably a recent randomized controlled trial reported efficacy of HBO in patients with CRPS.[11] The efficacy of HBO for IC might be explained by the reduction of ischemic conditions of the pelvic region and within the IC affected bladder wall.

Peripheral, sacral and pudendal nerve stimulation have been reported to ameliorate the symptoms of IC, albeit the posterior tibial nerve stimulation appears to be of inferior benefit compared with more centrally located neural targets.[12,13] However, increasing in vivo evidence suggests, that HBO has impact on pelvic neural structures as well and may induce improvement of neuronal function implying a further potential mechanism of action for IC. Cundall et al reported 13 patients with chronic pudendal neuropathy and fecal incontinence. They received 30 treatments of HBO during 6 weeks. Each treatment was at 2.4 ata breathing pure oxygen for 90 minutes. Pudendal latencies were performed sequentially throughout the treatment and 1 and 6 months after it had finished. Significant consistent improvement of pudendal nerve latencies developed in all patients and resulted in significantly improved incontinence.[14] Eguiluz et al and others reported clinical, electrophysiological, electromyographical and histological regeneration of the sciatic nerve in rats following neural impairment and subsequent HBO application.[15,16] Whether HBO directly stimulates axonal outgrowth and/or improves the electrophysiological properties by preventing ischemic fiber degeneration remains unclear at present. However, the observed regenerative and stabilizing effect on neural function may promote the clinical efficacy of HBO.

HBO treatment is usually well tolerated. Adverse effects, including visual disturbances, eustachian tube dysfunction and claustrophobia, are typically transient in nature and do not interfere with the patient's daily activities.[17] Only 1 complication probably related to therapy was noted in our cohort and led to the patient's dropping out. A short episode of disorientation developed in 1 patient for less than a minute during treatment session 7, which was initially suspicious of mild oxygen intoxication. However, the arterial oxygen tension at the time of the incident was 865 mm Hg, ie within the normal therapeutic range during HBO treatment session. Neurophysiological evaluation revealed residual signs of an increased convulsibility most probably related to an irregular intake of 50 mg amitriptyline that had not been declared by the patient before start of treatment. Although study continuation would have been feasible with close neurological monitoring, this patient was excluded from the study.

In our study efficacy of treatment appeared to follow an all-or-none rule, ie all patients reporting no improvement at all on GRA came out of the treatment series without any amelioration of symptoms and no late onset of efficacy within 3 months after end of treatment could be observed in this patient group. Moreover, patients with an initially excellent response to treatment appeared to benefit longer from HBO treatment. However, a retrospective subgroup analysis could not reveal clinical characteristics or symptom patterns that might allow prediction what patient might benefit best in what symptom domain. Moreover, the various forms of baseline medication, that could affect the outcomes, were equally distributed among the groups. During the study none of the patients received bladder instillations, which might exert influence on the epithelium, eg dimethyl sulfoxide, heparinoids or other glycosaminoglycan substitution compounds. Regarding the discordant peak amelioration of the various symptoms throughout followup we were unable to identify a potential underlying clinical pattern. Thus, we looked for previous reports of this phenomenon in trials on chronic radiation cystitis, since HBO has already been used extensively and successfully for the treatment of this condition that shows correspondence to interstitial cystitis regarding various histological alterations and symptoms.[1] Symptoms commonly associated with both bladder diseases include urinary frequency, urgency, incontinence, and pelvic pain. Several investigators have studied the use of HBO in patients with radiation cystitis and reported remarkable response rates regarding the reduction of pelvic pain, irritative voiding symptoms, particularly urgency, and gross hematuria.[18] However, the entire literature on HBO for radiation cystitis leaves the reader with the impression that, in contrast to our observation, the time course and extent of amelioration was homogenous for the entire range of the aforementioned radiation induced symptoms.

We observed a placebo rate of 0% and, thus, unblinding as a potential cause for this observation has to be discussed. However, we hesitate to attribute the observed placebo rate to potential unblinding. While it is generally possible in every placebo controlled study that unblinding to an uncertain degree might have been present (and not detected), factors related to the pressurization or the pressure chamber are highly unlikely to be the cause. All chamber instruments that could have been in the sight of the patients or could have been potentially accessible for them were strictly blinded. The human senses are not able to distinct between pure oxygen and normal unpolluted environmental air provided for breathing. Finally, even the sham group experienced the feeling of compression within the chamber. The chamber valves that regulate the air supply are pressure sensitive. Providing the patient with air is technically linked to a slight increase of chamber pressure. However, the tympanum and middle ear have a low threshold regarding barometric changes but cannot easily discriminate between mild and intense pressure increase under repetitive decompression via the eustachian tube. Thus, the technically required slight increase of chamber pressure is more likely to counteract unblinding, which might have resulted from the patient's impression that he was not exposed to hyperbaric conditions, than to promote unblinding.

The major limitation in interpreting our data is the small patient number resulting from the complexity and the time load of the intervention, making generalizability difficult. To reach sufficient statistical power to detect further differences between groups would require a multicenter protocol involving institutions with expertise in the fields of HBO and IC. Despite a 33% chance to receive sham treatment during 5 weeks the treatment compliance was excellent. Only 1 patient dropped out of the study due to unsteady attendance at the allocated treatment appointments. Verum treatment free of charge was offered to all potential control patients during recruitment and was a vital aspect of informed consent. The opportunity to receive a novel treatment that comes without significant side effects on bladder structure or function, which may be seen with other therapies for interstitial cystitis such as dimethyl sulfoxide or

hydrodistention, appeared to increase patient motivation to enter a time-consuming trial and to adhere to the protocol.

The major disadvantages of HBO are that is time-consuming and it has high costs.[19] Therefore, we believe that this treatment requires more extensive investigation before it can be routinely recommended for IC. At our institution we currently offer HBO to those patients who wish a noninvasive therapeutic approach and are able to spend at least 5 consecutive weeks on treatment. Finally, for patients with a favorable, long-term response to HBO and previous exhaustive conservative treatments, repetitive HBO treatment series appear to be a therapeutic alternative to cystectomy, which currently serves as the ultimate treatment for intractable interstitial cystitis resistant to conservative therapy.[20]

CONCLUSIONS

A total of 30 treatment sessions of HBO appear to be a safe, effective and feasible therapeutic approach for a subset of patients with IC whose clinical characterization and identification remain difficult before the start of treatment. In the treatment responders application of HBO resulted in a sustained decrease of IC symptoms compared with normobaric, normoxic sham treatment. A discordant profile regarding the peak amelioration of the various distinguished symptoms of the disease was observed. The therapeutic potential of an extended HBO series of more than 30 sessions or additional booster series remains to be elucidated.

Abbreviations and Acronyms

ata	=	atmosphere absolute
CRPS	=	complex regional pain syndrome
GRA	=	global response assessment
HBO	=	hyperbaric oxygenation
IC	=	interstitial cystitis
ICSI	=	Interstitial Cystitis Symptom Index
SC	=	sham control
V	=	verum treatment
VAS	=	visual analog scale

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