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Hyperbaric Oxygen for the Treatment of Interstitial Cystitis: Long-Term Results of a Prospective Pilot Study

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Abstract

Objective: We conducted a prospective pilot study to assess the safety and efficacy of hyperbaric oxygen (HBO) for the treatment of interstitial cystitis (IC).

Methods: Six patients underwent 30 sessions of 100% oxygen inhalation in a hyperbaric chamber and were followed up over 15 months. The measures of efficacy were changes in pain and urgency (visual analog scales), alteration in the patient's assessment of overall change in his well-being (Patient Global Assessment Form), and changes in frequency and functional bladder capacity (48-hours voiding log). Evaluation of symptom severity regarding pain and voiding problems was done using the O'Leary-Sant index.

Results: Four patients rated the therapeutic result as either excellent or good and assessed their well-being after HBO treatment as improved. Two patients showed only short-term amelioration of some of their symptoms. At 12 months follow-up the baseline functional bladder capacity increased from 37–161 ml (range) to 160–200 ml in the responder group. The 24-hour voiding frequency decreased from 15–27 to 6–11 voids per day, a pain scale improvement from 20–97 mm at baseline to 3–30 mm at 12 months follow-up and an urgency scale improvement from 53–92 mm to 3–40 mm, respectively was observed at 12 month follow-up. The symptom and pain index score decreased from 23–35 at baseline to 3–17 at 12 months follow-up.

Conclusion: HBO appears to be effective to treat IC patients. Treatment was well tolerated and resulted in a sustained decrease of pelvic pain and urgency, improvement of voiding patterns and increase of functional bladder capacity for at least 12 months.

Keywords: Interstitial cystitis; Hyperbaric oxygenation; Clinical trial

1. Introduction

Interstitial cystitis (IC) is a chronic and debilitating bladder syndrome, primarily affecting women, characterized by pelvic pain associated with urinary urgency, frequency and sterile, cytologically normal urine. Despite a large number of purported therapeutic approaches [1,2] the treatment of interstitial cystitis remains sub-optimal and the majority of those treatment modalities are lacking efficacy [3].

Hyperbaric oxygen (HBO) treatment of urology patients has gained greater clinical recognition during the last 15 years. It has already been used extensively and successfully for the treatment of chronic radiation cystitis [4,5] which shows correspondence to interstitial cystitis regarding symptoms, various histological alterations [6] and therapeutic approaches. In late stage disease, acute and chronic ischemia of the bladder wall occurs as described for the IC affected bladder [7,8]. Symptoms commonly associated with both bladder diseases include urinary frequency, urgency, incontinence and pelvic pain [9]. Many patients suffering from either radiation cystitis or interstitial cystitis develop a significant reduction in bladder capacity

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secondary to fibrosis of the bladder wall [1,6]. Not surprisingly, sodium pentosanpolysulfate has been shown to be effective in treating the diseased bladder of both interstitial cystitis and radiation patients [10,11].

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 [7,12–17]. The encouraging results of HBO treatment for radiation cystitis in addition to the correspondence of histological alterations and clinical characteristics between both bladder diseases led us to conduct a prospective observational pilot study of HBO in IC patients.

Technically the delivery of hyperbaric oxygen occurs when the patient rests the whole body and breathes 100% oxygen in a treatment chamber which is pressurized to higher than sea level, for example greater than 1 atmospheres absolute (ata.). Pressurization between 1.4 and 3.0 ata. while the patient inhales oxygen meets the *Undersea and Hyperbaric Medicine Society* definition of hyperbaric oxygen treatment [4].

2. Patients and methods

The study comprised 1 male and 5 female patients (age: 51.5 ± 15.1 years, duration of symptoms prior to treatment: 5.1 ± 3.1 years; means $\pm$ standard deviation) who all met the symptom criteria of the National Institute of Diabetes, Digestive and Kidney Diseases for IC (Table 1) [18]. All patients had previous conservative medical treatment, e.g. hydrostatic distension, intravesical instillation of dimethylsulfoxide, hyaluronic acid or oral medication (e.g. anticholinergics, antiallergics, sodium pentosanpolysulfate), which at best achieved short symptomatic relief. All patients received 30 treatment sessions of 100% oxygen inhalation via a facial mask at 2.4 ata. for 90 minutes in a multiplace hyperbaric chamber. Treatment was given in daily sessions, 6 days a week over a treatment period of 5 weeks. For managing urge incontinence while resting in the chamber the patients were instructed to wear pads during treatment. Although feasible anytime, no patient asked for a premature check out from the chamber due to unrestrained urinary urgency prior to the regular end of the treatment session.

All patients were interviewed and their clinical records reviewed. The measures of efficacy were changes from baseline in pain and urgency (100 mm visual analog scales (VAS)) and the patient's assessment of overall change in his well-being (Patient Global Assessment Form). Each patient was able to rate his overall well-being as improved, not changed, or worse since the start of HBO treatment. The measure of overall change in the patient's well-being as a measure of treatment efficacy takes into consideration the complex of symptoms associated with interstitial cystitis (e.g. frequency, urgency, dyspareunia) and the variable nature of the individual symptoms. Additionally, patients were requested to rate their satisfaction with the therapeutic outcome as either excellent, good, fair or poor. Further measures of efficacy addressed changes in 24-hr frequency and functional bladder capacity (48-hours voiding log). Evaluation of symptom severity regarding pain and voiding problems was done using the validated, self-administered O'Leary-Sant IC symptom and problem index (ICSI) [19]. This index comprises 8 questions assessing major pain and voiding symptoms. The maximum index score-sum of 35 points reflects maximum symptom and problem severity and the lowest possible score-sum is 0 points. Changes in all parameters were monitored and evaluated at 3 months intervals over a follow-up period of 15 months after completion of HBO treatment to assess any sustained effect from treatment.

Bladder biopsy specimens were available from all patients at baseline and were used for the histopathological classification of the patients into the two subtypes suggested for the disease: the *ulcerative or classic* IC, typically presenting with urothelial spongiosis and detachment, subepithelial, perineural and perivascular deposits of mononuclear cells, and an increased mast cell density predominantly in the lamina propia and detrusor muscle and the *non-ulcerative* IC, lacking the above inflammatory signs and showing no or less pronounced mast cell involvement [1].

3. Results

Of all 6 patients 4 rated the therapeutic result as either excellent or good and assessed their overall well-being after HBO treatment as improved (Table 1). In the following these 4 patients will be referred to as

Table 1
Selected patient demographic and clinical characteristics at baseline and classification of patients as responders or non-responders according to patient satisfaction and clinical outcome of HBO at 12 months follow-up

Pat.	Sex	Age (Years)	Symptom duration (Years)	Bladder capacity on awake cystometry	Onset of intense urge to void with 30 cc fill rate/min	Involuntary bladder contractions on cystometry	Satisfaction with outcome	Overall well-being after HBO treatment	Treatment recommendation by patient	Response to HBO	IC Subtype based upon hydrodistension	IC Subtype based upon histopathology
1	f	37.9	1.5	110 ml	80 ml	None	Good	Improved	Yes	Responder	n-u.	cl.
2	f	75.2	8.2	≤30 ml	Immediately	None	Excellent	Improved	Yes	Responder	cl.	cl.
3	f	53.8	7.3	125 ml	95 ml	None	Good	Improved	Yes	Responder	cl.	n-u.
4	m	47.3	6.3	100 ml	85 ml	None	Excellent	Improved	Yes	Responder	cl.	cl.
5	*f*	*34.4*	*1.1*	*100 ml*	*75 ml*	*None*	*Poor*	*No change*	*No*	*Non-responder*	*n-u.*	*cl.*
6	*f*	*60.6*	*6.2*	*100 ml*	*80 ml*	*None*	*Poor*	*Worse*	*No*	*Non-responder*	*cl.*	*cl.*

Classification of patients with regards to the subtypes of the disease (n-u.: non-ulcerative, cl.: classic, data of non-responders in *italics*). f: female, m: male.

''responders''. Two patients showed only short-term amelioration of some of their symptoms and were thus not satisfied with their therapeutic result at 3 month follow-up (''non-responders''). Both non-responders asked for alternative treatment and were subsequently not longer followed up. All 4 responders recommended HBO for treatment of IC symptoms (Table 1).

HBO treatment achieved a decrease of urinary frequency in all 4 responders (Table 2). The 24-hour voiding frequency decreased from a baseline range of 15–27 to a range of 6–11 voids per day at 12 months follow-up. Nocturia decreased from a baseline range of 2–7.5 voids per night to a range of 0–1.5 nighttime voids at 12 months follow-up, and patient no. 3 reported a sustained decrease of nocturia at 15 months follow-up. Baseline functional bladder capacity ranged from 37–161 ml in the responder group and HBO treatment resulted in a bladder capacity ranging from 160–200 ml in these patients at 12 months follow-up: 3 patients noted an increase in bladder capacity of more

Table 2
Changes in symptoms from baseline to 15 months follow-up

Parameter	Pat.	Baseline	End of HBO	3 months follow-up	9 months follow-up	12 months follow-up	15 months follow-up
24-hr frequency	1	21	15	11	8	8	13
	2	27	7	6	6	6	7
	3	15	12	11	10	10	12
	4	15	12	11	11	11	11
	5	*17*	*22*	*25*	–	–	–
	6	*22*	*16*	*25*	–	–	–
Nocturia (no. of voids)	1	4	1.5	0	0	0	2
	2	7.5	2	2	1	1	2
	3	2	0	0	0	0	1
	4	5	1.5	1.5	1.5	1.5	1.5
	5	*3*	*2*	*3*	–	–	–
	6	*3*	*3*	*3.5*	–	–	–
Bladder volume (ml)	1	124	161	155	211	200	121
	2	37	159	164	195	200	213
	3	161	190	177	189	196	166
	4	100	155	162	160	160	160
	5	*113*	*125*	*120*	–	–	–
	6	*103*	*141*	*120*	–	–	–
Pain (mm on VAS)	1	55	35	20	20	20	50
	2	97	3	3	3	3	3
	3	75	60	45	30	30	48
	4	20	8	8	3	8	8
	5	*30*	*0*	*0*	–	–	–
	6	*62*	*60*	*80*	–	–	–
Urgency (mm on VAS)	1	80	45	20	20	20	60
	2	92	10	3	0	3	10
	3	65	45	40	3	30	39
	4	53	41	40	40	40	40
	5	*90*	*70*	*80*	–	–	–
	6	*60*	*60*	*80*	–	–	–
ICSI score-sum	1	26	16	16	10	10	24
	2	35	5	3	1	3	8
	3	26	16	10	8	9	16
	4	23	16	17	17	17	17
	5	*26*	*21*	*27*	–	–	–
	6	*28*	*23*	*25*	–	–	–

Follow-up of the two non-responders (patients 5 and 6) was terminated after 3 months (data of non-responders in *italics*).

than 60% (patients nos. 1, 2, 4) including a maximum increase of 440% in patient no. 2 (Table 2). After HBO treatment all 4 responders experienced decrease of pain and urgency. The responders reported a pain scale improvement from a range of 20–97 mm at baseline to 3–30 mm at 12 months follow-up, and an urgency scale improvement from 53–92 mm to 3–40 mm respectively (Table 2). Patient no. 2 who initially suffered from most severe pain and urgency (symptom intensity of 97 mm on pain-VAS and 92 mm on urgency-VAS) reported almost complete relief from both conditions over the entire follow-up period (3 mm and 10 mm respectively at 15 months follow-up) (Table 2). All 5 female patients were sexually active at evaluation. One woman (patient no. 2) reported severe interstitial cystitis related dyspareunia, a second woman experienced mild dyspareunia (patient no. 1). Both patients reported complete relief from pain during sexual intercourse at 12 months follow-up. The symptom and problem index score correspondingly decreased among the responders from a baseline range of 23–35 points to 3–17 points at 12 months follow-up (Table 2). Again patient no. 2 showed the most beneficial outcome with a decrease from the maximum score-sum of 35 points at baseline to 3 points at 12 months and 8 points at 15 months follow-up.

At the end of HBO treatment all 4 responders reported a strong amelioration of symptoms compared to baseline and experienced either a stable (patient no. 4) or even escalating (patient nos. 1–3) amelioration during the following 12 months of follow-up. At 15 months follow-up patient no. 4 still reported sustained amelioration of all his symptoms. However, at that time patients no. 1 and no. 3 reported a general increase of symptom intensity compared to 12 months follow-up, whereas patient no. 2 only showed a mild relapse of particular symptoms, mainly urgency and increase of ICSI score-sum (Table 2).

No adverse events were observed. One woman reported mild eustachian tube dysfunction during 24 treatment sessions, resulting in a transient hearing impairment within the chamber. No medication was required for this condition. Oral medication was given to control temporary claustrophobia in one patient and to manage preexisting mild arterial hypertension in a second women.

4. Discussion

The biological effect of HBO derives from hypersaturating circulating plasma with dissolved oxygen during and shortly after treatment. This results in a transiently increased diffusion gradient between the circulation and surrounding tissues, driving transport of oxygen into the interstitium and tissues. At 3.0 ata. with 100% oxygen—the highest oxygen partial pressure used in clinical practice—arterial oxygen partial pressure may reach 1900 to 2100 mmHg while dissolved oxygen content may achieve 6.8 volumes percent (i.e. 6.8 ml oxygen per 100 ml blood). In contrast the normal value for oxygen content while breathing normal, 1 ata. pressurized air is 0.3 volumes percent. i.e. under HBO treatment a twohundredfold increase in the amount of dissolved oxygen might be achieved. Thus, HBO treatment leads to a net gain in oxygen concentration in tissues and subsequently enhances leukocyte function in part by phagocytic killing [20], induces neovascularisation [14,21], promotes wound healing and restores tissue homeostasis [22]. As a result, healthy granulation tissue starts growing [14,21].

Histologically, chronic radiation cystitis presents with telangiectasia, submucosal hemorrhage, interstitial fibrosis an eventual smooth muscle fibrosis [6]. In late stage disease, the urothelium becomes hypoxic and hypovascular and finally chronic ischemia of the bladder wall occurs [7]. Similar observations have been made for the IC affected bladder: Rosamilia described a decreased microvascular density [23] and other authors discussed ischemia of bladder wall in IC [24,25]. Fibrosis of the bladder wall in IC occurs frequently and has been attributed by Fall and Peeker to the classic, ulcerative type of IC [1]. According to the characterization of the two IC subtypes suggested by these authors radiation cystitis would compare to the classic but rather not to the non-ulcerative subtype leading to the hypothesis that the patient presenting with classic IC might respond favorably to HBO. However, in our series 1 responder (patient no. 1) was classified as a non-ulcerative IC patient based upon cystoscopy and hydrodistension, and patient no. 3 (responder) showed characteristics of the non-ulcerative subtype of IC in regards to histopathological findings within bladder biopsies (Table 1). Vice versa, non-responder no. 6 both cystoscopically and histologically presented with signs of classic IC but did not benefit from HBO. Collectively, our small pilot series does not support the assumption that patients suffering from the late stage, classic type of IC might uniformly benefit stronger from HBO treatment compared with patients presenting characteristics of the early, non-ulcerative disease. Moreover, our data does not give conclusive evidence that the mechanism of action of HBO is connected with bladder wall fibrosis and/or extend of inflammatory processes within the bladder wall, i.e. stage or subtype of IC.

Several studies on HBO treatment for radiation cystitis suggest that a better outcome will be observed if oxygenation is commenced soon after onset of bladder symptoms [5]. In contrast, our pilot series shows the best therapeutic result in the patient presenting with the longest history of symptoms (patient no. 2) and leaves the women with the shortest duration of symptoms unsatisfied (patient no. 5) (Table 1). Moreover, responders and non-responders did not appear to differ in age, previous or current medication or concomitant diseases. In conclusion, regarding the demographic and clinical data at baseline our series does not allow prediction what patient will benefit from HBO treatment. A larger randomized clinical trial encompassing a sufficient amount of patients with both IC types might clarify the significance of disease stage and clinical presentation of the patient for the efficacy of HBO.

Nocturia has been characterized as one of the most bothersome of all urological symptoms and is one of the cardinal features of IC [26]. Previous prevalence studies have typically defined nocturia as $\geq$2 voids per night and incremental increases in the number of nighttime voids have shown negative effect on sleep, symptom bother and health-related quality of life in general [26]. Thus, sustained treatment of this condition has most likely contributed significantly to the satisfaction of the 4 responders, who all—in contrast to the non-responders—reported cessation of this condition at 12 months follow-up.

Regarding both the response rate and response duration, a comparison of our pilot series with the results of HBO for radiation cystitis is not easy facing the different amount of outcome data available for both indications and different treatment regimens and outcome measures used: To date case series of radiation induced cystitis treated with HBO have been reported from 14 institutions in 5 countries, encompassing a total of 225 patients [17]. Treatment times range from 60 min–120 min per session and the applied chamber-pressure ranges from 2.0–3.0 ata. With a mean response rate of 82% (184 of 225 patients) 14 of the 15 authors concluded that HBO is an effective therapy for intractable radiation cystitis. However, the extent and duration of the response to HBO was in all but 2 studies [16,17] strictly correlated to cessation or reduction and relapse of symptomatic gross hematuria and at no time to amelioration of pain and irritative voiding symptoms as done in our study on IC. Treatment of hematuria was achieved in the aforementioned studies with various numbers of HBO sessions ranging from 9–68 treatments. The mean follow-up of the studies ranged from 4–61 months, revealing an overall mean response duration of 23.9 months (range: 1–102 months). In summary, with disregard to the divergent study protocols and outcome measures among the various studies, both the response rate and the duration of response observed in our study were less pronounced compared with those seen for HBO in radiation cystitis.

Since this is a pilot study, a putative placebo effect has to be discussed. A placebo response ranging from 15%–30% in IC has been repeatedly observed [27]. Moreover, case series are generally difficult to evaluate, particularly in a disease such as IC that is both defined and characterized primarily by symptoms. However, we observed a sustained homogeneous amelioration of a range of symptoms over a period of at least 12 months in 3 responders and over a 15 month follow up interval in patient no. 4. If the observed relapse of particular symptoms at 15 months follow-up in patients nos. 1–3 reflects a waning of either treatment effect or placebo response remains unclear. However, a continuous placebo response of IC patients over a period of 12 months has not been observed at our institution before and has previously not been reported to our knowledge, strongly suggesting a long-term effect of HBO in the 4 responders.

HBO treatment is usually well tolerated. Adverse effects, including visual disturbances, eustachian tube dysfunction and claustrophobia, are uncommon [12–15]. Only one complication related to barometric pressure changes was noted in our cohort of patients: Eustachian tube dysfunction exclusively occurred during treatment sessions and did not interfere with the patient's daily activities. Eustachian tube dysfunction is one of the most common side effects of HBO and typically results in a transient hearing impairment strictly during the treatment sessions within the chamber. It predominantly occurs within the first minutes of increasing the chamber pressure and during the fall of the chamber pressure at the end of the treatment session. Usually the problem can be 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. Occasionally a decongesting nasal spray (e.g. xylometazoline) is required and administered some minutes prior to start of and/or during treatment. Regarding adverse events, a general advantage of HBO treatment is the absence of significant side effects on bladder structure or function, which may be seen with other therapies for interstitial cystitis, such as intravesical dimethyl-sulfoxid (DMSO) or hydrodistension [28,29].

For patients with a favorable, long-term response to HBO repetitive 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 [30]. In

contrast to surgery, HBO is noninvasive but on the other hand might not compare favorably to the cost of surgery in the long term regarding repetitive treatment series: The estimated cost of HBO treatment in Germany is 150–250 Euro per session resulting into a total cost of 4500–7500 Euro for a series of 30 treatment sessions [5]. Thus, cost considerations make it difficult to recommend HBO as either a first-line treatment modality or cost-related alternative to surgery. However, in an effort to preserve the urinary bladder as long as possible the use of HBO for interstitial cystitis should be considered prior to surgery.

5. Conclusions

HBO appears to be effective to treat IC patients suffering from interstitial cystitis. Treatment was well tolerated and resulted in a sustained decrease of pelvic pain and urgency, improvement of voiding patterns and increase of functional bladder capacity for at least 12 months. This pilot study served as "*proof of principle*" and a randomized, placebo-controlled study is currently performed to provide evidence-based data on the efficacy of this novel therapeutic approach to IC.

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