Pain Medicine, 22(6), 2021, 1324–1332
doi: 10.1093/pm/pnaa416
Advance Access Publication Date: 16 February 2021
Original Research Article

Evaluation of a Hyperbaric Oxygen Therapy Intervention in Individuals with Fibromyalgia

K. Curtis, PhD,* J. Katz, PhD,[†,‡] C. Djaiani, BSc,[§] G. O'Leary, MD, FRCPC,[‡] J. Uehling, MS, CCRP,[§] J. Carroll, BHA,[‡] D. Santa Mina, PhD,[‡,¶] H. Clarke, MD, PhD, FRCPC,[‡,§] M. Gofeld, MD, PhD, FRCPC,[‖] and R. Katznelson, MD, FRCPC[‡,§]

*Toronto Western Hospital, University Health Network, Toronto, Ontario; [†]Department of Psychology, York University, Toronto, Ontario; [‡]Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, Toronto, Ontario; [§]Hyperbaric Medicine Unit, Toronto General Hospital, University Health Network, Toronto, Ontario; [¶]Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario; [‖]Silver Medical Group, North York, Toronto, Ontario, Canada

Correspondence to: Rita Katznelson, MD, FRCPC, Hyperbaric Medicine Unit, Toronto General Hospital, 200 Elizabeth St, Toronto, ON, M5G2C4, Canada. Tel: 416-340-4800 ext. 6873; Fax: 416-340-4481; E-mail: rita.katznelson@uhn.ca.

Funding sources: Funding for this study was received from the Department of Anesthesia and Pain Management, University Health Network, Toronto, Ontario, Canada.

Conflicts of interest: None of the authors declare any conflicts of interest.

Trial registration: ClinicalTrials.gov identifier NCT02467218.

Abstract

Objective. To evaluate the feasibility and safety of hyperbaric oxygen therapy (HBOT) in patients with fibromyalgia (FM). **Design**. A cohort study with a delayed treatment arm used as a comparator. **Setting**. Hyperbaric Medicine Unit, Toronto General Hospital, Ontario, Canada. **Subjects**. Eighteen patients diagnosed with FM according to the American College of Rheumatology and a score $\geq$60 on the Revised Fibromyalgia Impact Questionnaire. **Methods**. Participants were randomized to receive immediate HBOT intervention (n = 9) or HBOT after a 12-week waiting period (n = 9). HBOT was delivered at 100% oxygen at 2.0 atmospheres per session, 5 days per week, for 8 weeks. Safety was evaluated by the frequency and severity of adverse effects reported by patients. Feasibility was assessed by recruitment, retention, and HBOT compliance rates. Both groups were assessed at baseline, after HBOT intervention, and at 3 months' follow-up. Validated assessment tools were used to evaluate pain, psychological variables, fatigue, and sleep quality. **Results**. A total of 17 patients completed the study. One patient withdrew after randomization. HBOT-related adverse events included mild middle-ear barotrauma in three patients and new-onset myopia in four patients. The efficacy of HBOT was evident in most of the outcomes in both groups. This improvement was sustained at 3-month follow-up assessment. **Conclusion**. HBOT appears to be feasible and safe for individuals with FM. It is also associated with improved global functioning, reduced symptoms of anxiety and depression, and improved quality of sleep that was sustained at 3-month follow-up assessment.

Key Words: Hyperbaric Oxygen; Fibromyalgia

Introduction

Fibromyalgia (FM) is a chronic pain disorder affecting 1.2% of the Canadian population [1]. It is characterized by widespread body pain and symptoms such as fatigue, cognitive impairment, disturbed (nonrestorative) sleep, depression, anxiety, stiffness, tenderness, and functional limitations [2]. FM is a potentially devastating disorder leading to disability, emotional distress, and significant personal, social, and economic burden [3].

The diagnosis of FM relies on an evaluation of the individual's self-reported symptoms, past medical history and physical examination, and the clinical judgment of

© The Author(s) 2021. Published by Oxford University Press on behalf of the American Academy of Pain Medicine.
All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

the assessing physician. The Canadian FM management strategy reflects the American College of Rheumatologists guidelines (2010), which established a revised assessment methodology for making a clinical diagnosis of FM [4]. Currently, FM has no known cure, and the treatment is directed toward symptom control, with goals of increased functionality in daily living, improved quality of life, and increased psychological well-being. The multimodal approach includes both pharmacological treatment and nonpharmacological interventions, such as education, psychological treatment, exercise or physical therapies, and alternative and complementary approaches, such as yoga and tai chi [2]. No single approach has demonstrated consistent efficacy across all variety of symptoms [5].

The Role of Oxygen in the Pathophysiology of FM

The cardinal symptom of FM is persistent, diffuse muscular pain, which resembles the muscle soreness that occurs after strenuous physical exercise and anaerobic muscle metabolism. There is evidence that impaired oxygenation and oxidative system abnormalities are associated with alterations in muscle metabolism and microcirculation, leading to pain [6–9]. It has also been reported that FM may be associated with abnormal tissue oxygen delivery [6], resulting in local muscle hypoperfusion, ischemia [7–9], low oxygen extraction fraction [10], and prolonged half-times of oxygenation recovery [10]. Muscle tissue ischemia, exacerbated by muscle contraction, is a powerful activator of unmyelinated muscle nociceptors that facilitates central sensitization in animal models [11]. Cellular mitochondrial dysfunction, decreased levels of muscle phosphocreatine and adenosine triphosphate, and low phosphocreatine/inorganic phosphate ratio contribute to sensitization of peripheral muscle nociceptors by intensifying pain, fatigue, and muscle weakness in patients with FM [12]. The role of oxygen delivery within the musculoskeletal system has both structural and functional implications for central and peripheral pain receptor sensitization, resulting in altered pain perception and processing [12], making oxygen delivery an important treatment target in patients with FM.

Hyperbaric Oxygen Therapy (HBOT) and FM

HBOT is a medical treatment defined as the administration of 100% oxygen at an ambient pressure higher than atmospheric pressure. The physiological effects of HBOT are based on a dramatic increase in the amount of dissolved oxygen carried in blood, with a subsequent effect of oxygenation of ischemic areas with compromised circulation. HBOT leads to a net gain in oxygen concentration in tissues, facilitates neovascularization and angiogenesis, restores tissue homeostasis, and enhances leukocyte function [13]. It also exhibits anti-inflammatory effects, promotes neuroplasticity, impacts mitochondrial functioning, and stimulates nitric oxide synthesis, which can reduce hyperalgesia and facilitate nitric oxide–dependent endogenous opioid release [14]. HBOT is widely considered to be a safe and reliable treatment modality for the variety of conditions such as air gas embolism, decompression sickness, carbon monoxide poisoning, necrotizing infection, delayed radiation injury, and complex wounds. It has few side effects, and the only one absolute contraindication is untreated pneumothorax.

A growing body of evidence indicates that HBOT may reduce pain and fatigue and improve global functioning and quality of life in patients with FM [15–17]. However, none of these studies used a follow-up evaluation to determine whether the positive gains resulting from HBOT were maintained over time.

Objectives

The objectives of the present study were to measure the safety and feasibility of HBOT, as well as the preliminary estimates of its effect on global functioning, psychological health, sleep, and fatigue, in patients with FM. The primary hypothesis was that HBOT would be feasible (>50% recruitment rate, >80% retention rate, and >80% treatment compliance) and safe (no serious adverse events precluding continued participation) for individuals with FM. The secondary hypotheses were 1) that participants in the HBOT group would demonstrate greater improvements in global functioning, psychological health, sleep quality, and fatigue from pre- to post-HBOT intervention over time (within-group analyses) and in comparison with control participants, and 2) that improvements in all variables would be maintained at a 3-month follow-up assessment.

Methods

Design

The present study was a single-center prospective cohort study evaluating an 8-week HBOT intervention (INT) compared with a waitlist control (WLC) group. The cohort study used a delayed treatment arm as a comparator, such that the control group received the intervention (HBOT) after a 3-month waiting period. The assessors involved in completing the assessments were blinded to participants' group assignments. The design and reporting of the present study followed the relevant aspects of the 2010 Consolidated Standards of Reporting Trials (CONSORT) statement. The study was approved by the Research Ethics Boards at the University Health Network (Research Ethics Board number 4-7888) and York University (Research Ethics Board approval certificate: e2015-249) and was registered at ClinicalTrials.gov (NCT02467218) before participant recruitment. Participant recruitment occurred between November 2015 and August 2017.

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

Sample

Eligible participants were those who were diagnosed with severe FM according to the American College of Rheumatology (2010) guidelines, were >18 years of age, and had a score ≥60 on the Revised Fibromyalgia Impact Questionnaire (FIQR) [18] during the baseline assessment. Exclusion criteria were a recent positive pregnancy test or planning to become pregnant during the study period; claustrophobia; seizure disorder; active asthma; chronic sinusitis; chronic or acute otitis media; current treatment with bleomycin, cisplatin, doxorubicin, or disulfiram; or participation in a concurrent investigative drug or device trial within the prior 30-day period. Potential participants were assessed in the hyperbaric unit by one of the hyperbaric physicians trained in chronic pain management to confirm the diagnosis of FM and rule out contraindications to HBOT.

Participants were recruited from the chronic pain clinics located in the Greater Toronto Area, Ontario, Canada. They were interviewed over the telephone by the study coordinator to determine eligibility. Eligible participants were provided with information about the nature of the study, the commitment required to participate, and the risks and benefits of participation, and if agreeable, they provided informed consent to participate.

The randomization schedule was completed by the study coordinator, using a computer-generated randomization code in predetermined block sizes of four. Before baseline testing, participants were randomly allocated 1:1 to either the INT or WLC group through the use of concealed opaque randomized envelopes containing group assignments.

HBOT Protocol

HBOT was provided in a multiplace chamber (Fink Engineering, Rectangular Hyperbaric Systems, Australia) for 90 minutes with 100% oxygen at 2.0 atmosphere absolute (ATA) with one 5-minute air break, once daily, five times per week for 8 consecutive weeks (40 treatments total). Each HBOT session was supervised by hyperbaric physicians. Participants were instructed to continue to take their regular medications and to continue to engage in all nutritional or exercise regimens and behavioral, massage, acupuncture, physical, or cognitive therapies as usual throughout the study period.

Feasibility Assessment

The primary objective of this study was to assess the feasibility of conducting an HBOT randomized controlled trial (RCT). Feasibility was assessed via recruitment, retention, HBOT adherence, and adverse event rates. Recruitment rate was calculated as the number of randomized patients divided by the number of eligible patients approached. Retention was assessed as the number of participants randomized divided by the number of participants retained to their final assessment (12 weeks after HBOT in both groups). HBOT adherence in both groups was expressed as a percentage reflecting the number of completed sessions divided by 40 (total number of sessions in the HBOT protocol). Treatment safety was assessed through the number and type of adverse events occurring during HBOT.

Assessment Timepoints

INT participants were assessed at baseline, 8 weeks (immediately post-intervention), and 20 weeks (12 weeks post-intervention). WLC participants were assessed at baseline, 12 weeks (end of waiting period), 20 weeks (end of HBOT), and 32 weeks (12 weeks post-intervention).

Outcome Measures

The FIQR is the currently recommended tool for multidimensional function assessment in individuals with FM [19]. It is a 21-item self-report measure that queries participants on symptoms and functional deficits. The first domain evaluates physical *function* and the ability to perform nine activities of daily living involving large muscle groups. Participants answer according to the degree of difficulty they experience, ranging from 0 (no difficulty) to 10 (very difficult). The second domain evaluates the *overall impact* of FM and contains two items asking about the general impact of FM on functional ability. These two items are answered on a scale from 0 (never) to 10 (always). The third domain evaluates ten FM-related *symptoms*, and these items are answered on a scale from 0 (no impairment) to 10 (maximum impairment). The total possible score is 100, which represents the maximum impact of FM on the individual.

The Hospital Anxiety and Depression Scale (HADS) [20] is a 14-item self-report questionnaire that measures anxiety (seven items) and depressive symptoms (seven items). For each item, participants are asked to select one from among four possible choices (scored from 0 to 3) that best describes how they have been feeling over the past week. The HADS yields an anxiety (HADS-A) and a depressive (HADS-D) symptom subscale score, each with a maximum total score of 21.

The Fatigue Severity Scale (FSS) [21] is nine-item measure widely used to assess fatigue across many chronic diseases and consists of quantifying the impact of fatigue on specific types of functioning over a 1-week period. Each item is scored on a seven-point scale, where 1 is "strongly disagree" and 7 is "strongly agree." The FSS score is calculated by averaging all items to yield a score from 1 to 7, with higher scores indicating more severe fatigue symptoms. Fatigue was also measured by a fatigue visual analog scale (VAS) that used the global severity of fatigue, ranging from 0 to 10, with 0 being "worst" and 10 being "normal".

The Jenkins Sleep Scale (JSS) [22] is a self-report questionnaire measuring sleep problems over the most recent month. It contains four items evaluating trouble falling

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

asleep, trouble staying asleep, waking up several times, and awakening unrefreshed. Each item is scored on a six-point Likert scale from 0 (not at all) to 5 (22–31 days), with scores ranging from 0 to 20 and higher scores indicating more frequent sleep problems.

The Patient Global Impression of Change (PGIC) is a well-established outcome measure used in research trials evaluating interventions for individuals with FM and has been recommended by the Initiatives on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [23]. The PGIC assesses global response to treatment at one time interval (post-treatment) and has been associated with clinical outcomes (pain, vitality, sleep, physical function, and cognitive complaints) in patients with FM. Respondents are asked to rate overall improvement in symptoms according to a seven-point Likert scale with the following descriptors: 7= "very much improved," 6= "much improved," 5= "minimally improved," 4= "no change," 3= "minimally worse," 2= "much worse," and 1= "very much worse" [24]. We used a modified approach of the PGIC to evaluate the patient's perception of change and satisfaction. The following descriptors were used for each number: 1= "no change," 2= "almost the same," 3= "a little better," 4= "somewhat better," 5= "moderately better," 6= "better," and 7= "a great deal better."

Data Analysis

Participant demographics and disease characteristics were summarized with descriptive statistics (mean ± standard deviation or frequencies and percentages). Outliers were not excluded because of the small sample size, the pilot nature of this study, and the heterogeneity of the presentation of symptoms for individuals with FM. Within- and between-group changes in outcomes over time were assessed via linear mixed-effect models. Maximum likelihood estimations were used to estimate the adjusted sample mean scores for all of the outcomes. Between-group comparisons were conducted for INT and WLC from baseline to 8 weeks (end of HBOT) and 12 weeks (end of the waiting period), respectively. Models for each between-group analysis included a "group × time" as the fixed effect and individual participants as the random effect. Pairwise comparisons between timepoints for each group were adjusted with Tukey's honestly significant difference (HSD) test. To increase the precision of the within-group estimates of change in outcomes from before HBOT to 12 weeks after HBOT, the INT and WLC groups were combined and analyzed as a single group through the use of a linear mixed-effect model similar to the above. The PGIC was analyzed by using frequency of responses for the INT and WLC group (combined) at post-HBOT and 12 weeks after HBOT.

Results

The CONSORT diagram is shown in Figure 1. Thirty-three participants were assessed for eligibility, of whom seven were ineligible. Of the 26 patients approached, 18 agreed to participate (69.2% recruitment rate) and were randomized in a 1:1 ratio to INT (n = 9) or WLC (n = 9). One participant withdrew after randomization because of time constraints, and there was no further attrition (94.4% retention rate). INT and WLC participants completed 39.8 (±0.55) of the 40 HBOT sessions (99.5% HBOT adherence rate), although treatment completion data were not available for two participants. During exposure to HBOT, three participants were diagnosed with mild middle-ear barotrauma, and four participants reported new-onset myopia. All participants completed the study.

Participant demographic and clinical characteristics are presented in Table 1. There were no statistically significant differences between the INT and WLC groups.

Mean values at baseline, post-intervention (INT), and the end of the waiting period (WLC) and between-group comparisons in the delta from baseline in each group are presented in Table 2. The FIQR subscales and total score were lower in the INT group than in the WLC group ($P < 0.05$). HADS anxiety and depression scales were lower by 4.6 (95% confidence interval [CI]: –10.0 to 0.8; $P = 0.09$) and 4.9 (95% CI: –9.4 to –0.5; $P = 0.03$) in the INT group than in the WLC group. The JSS scores remained relatively stable between baseline and the end of HBOT for WLC participants (17.0 ± 1.5 vs. 16.5 ± 1.5). The INT group had an improvement in reported sleep problems by 4.4 points (95% CI: –8.6 to –0.2, $P = 0.04$) in comparison with the WLC group. Fatigue as measured by the FSS and VAS scores remained stable between timepoints for both groups.

Mean values per assessment and within-group changes from before HBOT to 12 weeks after HBOT in a total sample (INT and WLC) analysis are presented in Tables 3 and 4, respectively. FIQR total and all subscales, as well as HADS-Anxiety and HADS-Depression, were improved both from baseline to post-HBOT and from baseline to 12 weeks after HBOT ($P < 0.002$). Figure 2 shows the trend in scores across this period for these six outcomes. JSS scores decreased by 4.8 points (95% CI: 2.3 to 7.3; $P = 0.001$) from baseline to the post-HBOT timepoint and remained 2.4 points less than baseline at 12 weeks after HBOT (95% CI: –0.2 to 5.0; $P = 0.080$). Mean FSS scores remained constant within 1 point across all timepoints. Measurements on the fatigue VAS were 1.8 points higher at post-HBOT than at baseline assessment (95% CI: –4.5 to 0.9; $P = 0.254$), which was maintained at the evaluation 12 weeks after HBOT evaluation ($\Delta = -0.5$; 95% CI: –3.2 to 2.3; $P = 0.912$). There were negligible differences between the post-HBOT assessment and the assessment 12 weeks after

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

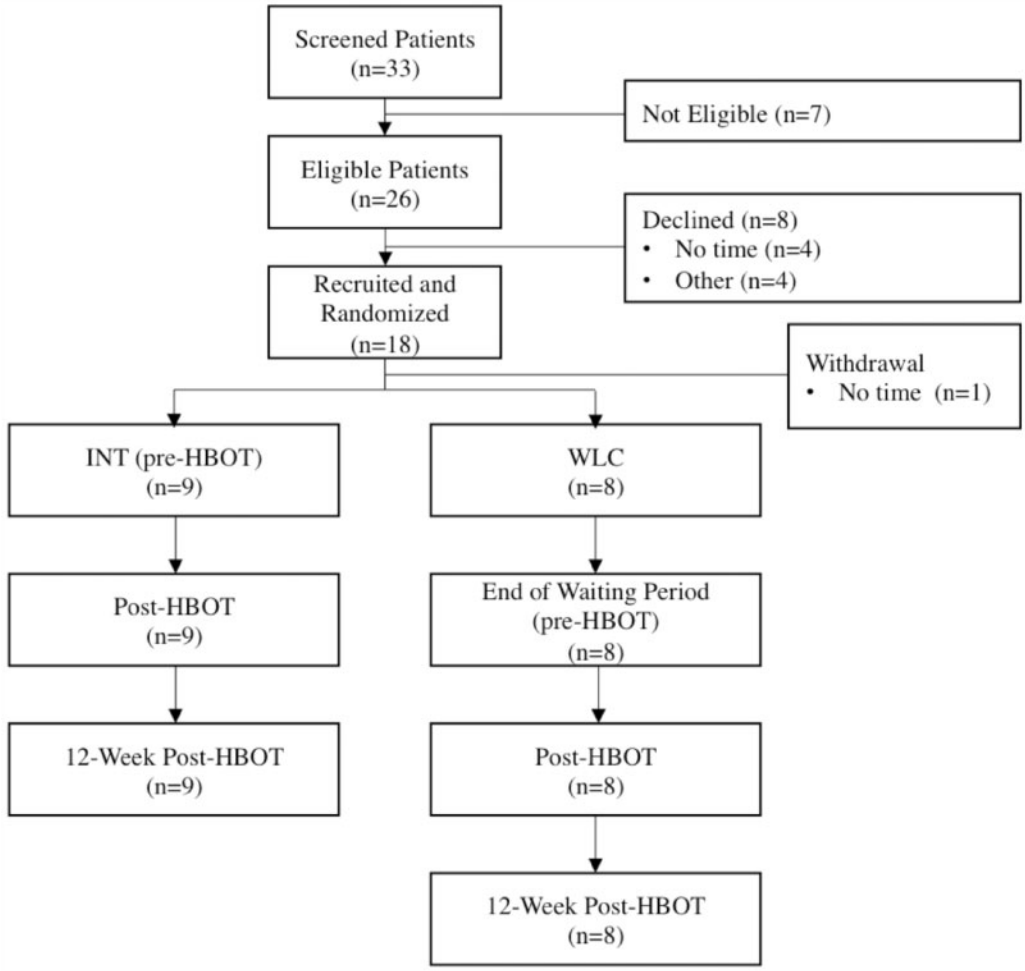

Figure 1. CONSORT diagram.

Table 1. Participants' characteristics

Variables	INT	WLC
Female	7 (77.8)	8 (100.0)
Comorbidities:		
Headache	8 (88.9)	5 (62.5)
Irritable bowel syndrome	2 (22.2)	4 (50.0)
Pelvic pain	5 (55.6)	4 (50.0)
Temporomandibular pain	5 (55.6)	5 (62.5)
Age, y	45.7 ± 14.2	51.8 ± 14.5
Weight, kg	69.5 ± 18.1	67.1 ± 10.7
Height, cm	166.3 ± 8.0	163.9 ± 5.3
Body mass index, kg/m^2	24.9 ± 5.3	25.0 ± 4.2
Chronic pain duration, mo	132.0 ± 115.8	272.1 ± 202.7

Data reported as number of participants (%) or mean ± standard deviation.

HBOT, indicating sustainable changes derived over the treatment period.

The PGIC assessments showed different degrees of improvement in symptoms in nine patients after HBOT and in 12 patients at the 3-month follow-up, respectively (Figure 3).

Discussion

Our study demonstrated the feasibility and safety of 8 weeks (5 days per week) of hyperbaric oxygen therapy in patients with FM.

We were also able to demonstrate a sustainable improvement in clinical outcomes that lasted for at least up to 3 months. Furthermore, we found an improvement in sleep quality in participating subjects that was confirmed by a well-validated sleep questionnaire.

Only one individual withdrew from the study after randomization was completed. The HBOT was tolerated well, with low incidence and severity of adverse events. Additionally, participants reported moderate global impressions of change indicating partial improvement of symptoms.

Individuals in the INT group fared better than those in the WLC group. FM-related symptoms and functional impairments, symptoms of anxiety and depression, and self-reported sleep were significantly improved in individuals with FM who participated in an 8-week HBOT intervention when compared with the WLC group. More importantly, the post-intervention improvements were sustained during a 3-month follow-up period. This study

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

Table 2. Baseline and second measurements in INT and WLC groups with between-group comparisons

Outcome	INT (Baseline)	WLC (Baseline)	INT (End of HBOT)	WLC (End of Waiting Period)	Δ INT–WLC (95% CI)	*P* Value
FIQR–activity	22.4 ± 2.3	21.1 ± 2.4	11.9 ± 2.3	19.9 ± 2.4	–8.1 (–14.8 to –1.3)	0.020
FIQR–overall impact	17.7 ± 1.8	17.6 ± 1.9	8.9 ± 1.8	14.9 ± 1.9	–6.0 (–11.2 to –0.8)	0.024
FIQR–symptoms	39.6 ± 3.0	41.4 ± 3.1	25.1 ± 3.0	38.3 ± 3.1	–13.2 (–21.9 to –4.5)	0.004
FIQR–total	79.7 ± 6.1	80.1 ± 6.5	45.9 ± 6.1	73.1 ± 6.5	–27.4 (–45.2 to –9.3)	0.004
HADS-Anxiety	12.1 ± 1.8	12.5 ± 1.9	7.8 ± 1.8	12.4 ± 1.9	–4.6 (–10.0 to 0.8)	0.094
HADS-Depression	10.4 ± 1.5	11.1 ± 1.6	7.4 ± 1.5	12.4 ± 1.6	–4.9 (–9.4 to –0.5)	0.031
JSS	16.8 ± 1.4	17.0 ± 1.5	12.1 ± 1.4	16.5 ± 1.5	–4.4 (–8.6 to –0.2)	0.040
FSS total	5.7 ± 0.5	6.2 ± 0.6	5.4 ± 0.5	6.5 ± 0.6	–1.07 (–2.7 to 0.5)	0.179
Fatigue VAS	5.3 ± 1.0	2.3 ± 1.0	4.2 ± 1.0	1.5 ± 1.0	2.7 (–0.1 to 5.6)	0.062

Table 3. Combined group (INT and WLC) means at pre-, post-, and 12 weeks post-HBOT (n = 17)

	Timepoint		
	Pre-HBOT	Post-HBOT	12 Weeks Post-HBOT
FIQR activity	21.2 ± 1.7	11.4 ± 1.8	13.8 ± 1.8
FIQR overall	16.4 ± 1.4	7.8 ± 1.4	7.5 ± 1.5
FIQR symptoms	39.0 ± 2.3	22.8 ± 2.3	26.0 ± 2.4
FIQR total	76.6 ± 4.7	42.1 ± 4.8	47.4 ± 5.0
HADS anxiety	12.2 ± 1.3	8.2 ± 1.3	9.1 ± 1.3
HADS depression	11.4 ± 1.1	6.9 ± 1.1	7.3 ± 1.2
JSS	16.6 ± 1.0	11.9 ± 1.1	14.3 ± 1.1
FSS total	6.1 ± 0.4	5.1 ± 0.4	5.3 ± 0.4
Fatigue VAS	3.5 ± 0.8	5.3 ± 0.8	4.0 ± 0.9

Table 4. Between-timepoint contrasts for the combined cohort of all HBOT treatments (n = 17)

Outcome and Contrast	Δ (95% CI)	*P* Value
FIQR activity		
Pre-HBOT to post-HBOT	9.8 (5.9 to 13.7)	<0.001
Pre-HBOT to 12 weeks post-HBOT	7.5 (3.3 to 11.6)	<0.001
Post-HBOT to 12 weeks post-HBOT	–2.4 (–6.5 to 1.9)	0.352
FIQR overall		
Pre-HBOT to post-HBOT	8.6 (5.0 to 12.2)	<0.001
Pre-HBOT to 12 weeks post-HBOT	8.9 (5.1 to 12.6)	<0.001
Post-HBOT to 12 weeks post-HBOT	0.3 (–3.5 to 4.1)	0.978
FIQR symptom		
Pre-HBOT to post-HBOT	16.2 (10.4 to 22.1)	<0.001
Pre-HBOT to 12 weeks post-HBOT	13.0 (6.9 to 19.1)	<0.001
Post-HBOT to 12 weeks post-HBOT	–3.2 (–9.4 to 3.0)	0.419
FIQR total		
Pre-HBOT to post-HBOT	34.5 (23.8 to 45.3)	<0.001
Pre-HBOT to 12 weeks post-HBOT	29.2 (17.9 to 40.5)	<0.001
Post-HBOT to 12 weeks post-HBOT	–5.3 (–16.7 to 6.0)	0.487
HADS anxiety		
Pre-HBOT to post-HBOT	4.1 (2.1 to 6.1)	<0.001
Pre-HBOT to 12 weeks post-HBOT	3.2 (1.1 to 5.2)	0.002
Post-HBOT to 12 weeks post-HBOT	–0.9 (–3.0 to 1.2)	0.536
HADS depression		
Pre-HBOT to post-HBOT	4.5 (2.1 to 6.9)	<0.001
Pre-HBOT to 12 weeks post-HBOT	4.0 (1.5 to 6.6)	0.001
Post-HBOT to 12 weeks post-HBOT	–0.4 (–3.0 to 2.1)	0.903
JSS		
Pre-HBOT to post-HBOT	4.8 (2.3 to 7.3)	<0.001
Pre-HBOT to 12 weeks post-HBOT	2.4 (–0.2 to 5.0)	0.080
Post-HBOT to 12 weeks post-HBOT	–2.4 (–5.0 to 0.2)	0.082
FSS total		
Pre-HBOT to post-HBOT	0.9 (0.03 to 1.7)	0.041
Pre-HBOT to 12 weeks post-HBOT	0.7 (–0.2 to 1.7)	0.181
Post-HBOT to 12 weeks post-HBOT	–0.2 (–1.2 to 0.7)	0.818
Fatigue VAS		
Pre-HBOT to post-HBOT	–1.8 (–4.5 to 0.9)	0.254
Pre-HBOT to 12 weeks post-HBOT	–0.5 (–3.2 to 2.3)	0.912
Post-HBOT to 12 weeks post-HBOT	1.3 (–1.5 to 4.2)	0.504

is the first trial that evaluated both post-intervention and follow-up time points after HBOT in individuals with FM.

The results from the present study are consistent with previous RCTs indicating improvements in FM-related functional impairments and global symptoms [16, 17]. These previous studies evaluated FM-related functional impacts through the FIQ, which captures the functional and overall subscales of the FIQ-R, as well as the Symptom Severity Scale. On the basis of the literature to date [16, 17, 25, 26], research supports the use of HBOT to reduce the impact of FM on functional activities and FM-related global symptoms. Addressing functional impairments and challenges in completing activities of daily living is a central goal in FM treatment and management.

Improvements in symptoms of anxiety and depression in our study are also consistent with a previous RCT evaluating HBOT for individuals with FM who have a history of childhood abuse, in comparison with a psychotherapy condition [17]. Furthermore, in another RCT [16], general psychological distress improved from pre- to post-intervention in individuals with FM who underwent HBOT as compared with a control condition, and in a single cohort study [25], anxiety scores improved from pre- to post-intervention in individuals with FM who underwent HBOT.

The present study is the first RCT to document between-condition improvements in sleep quality in

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

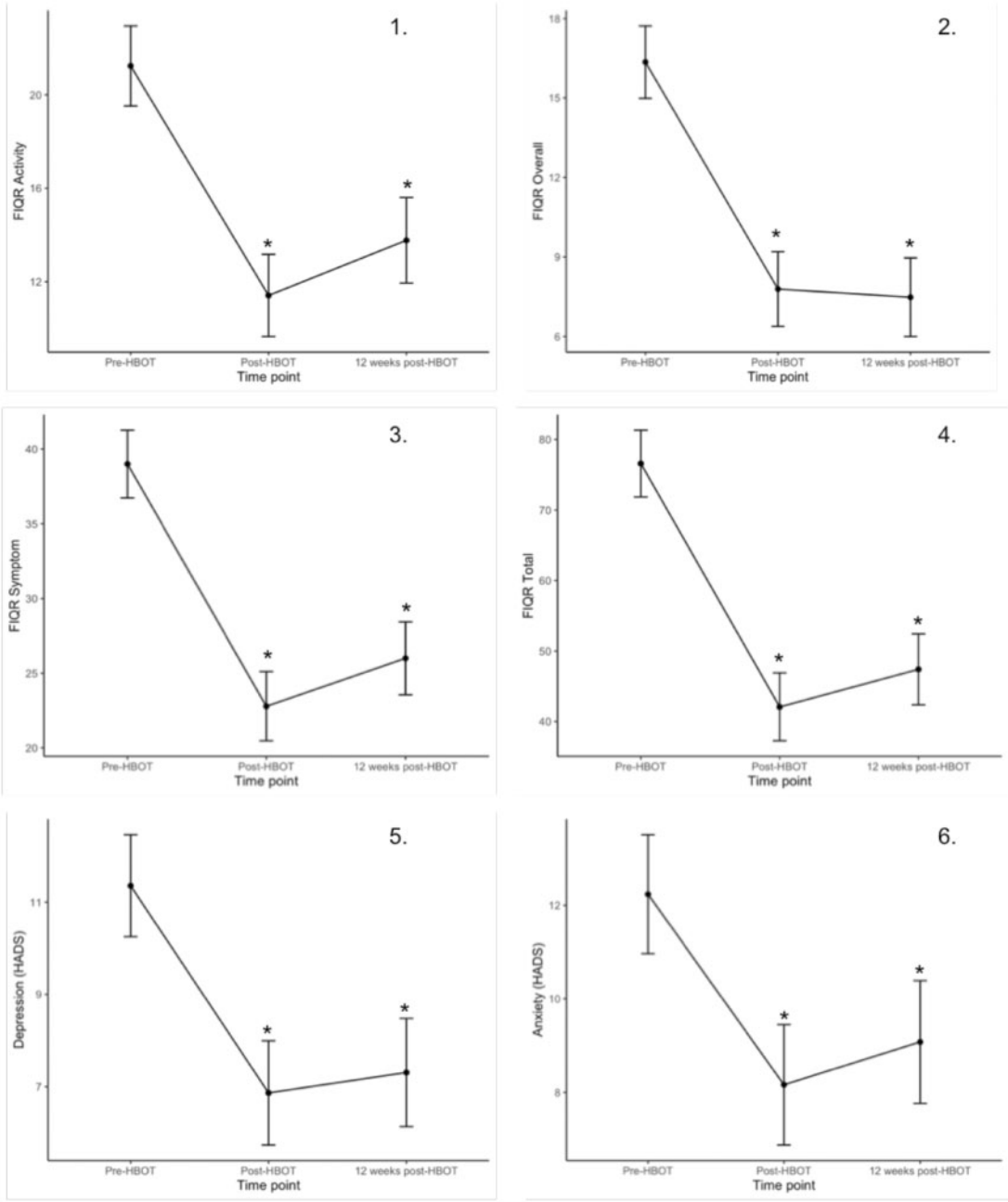

Figure 2. Changes in FIQR and HADS scores from pre-HBOT to post-HBOT and 12 weeks post-HBOT.

individuals with FM from pre- to post-HBOT intervention. Although one of the previous RCTs showed improvements in functionality for individuals with FM after HBOT on a self-reported measure of sleep quality (Symptom Severity Scale; "waking up unrefreshed"), it was related to the total score of FM symptoms and not specifically to the sleep quality [17]. Another study reported an improvement in quality of sleep but not the total hours of sleep per night after HBOT intervention by using the Pittsburgh Sleep Quality Index (PSQI) [26]. A different study using the same sleep assessment tool found no improvements in sleep quality [25]. The difference in results may be attributable to difference in protocols pertinent to duration of HBOT (a total of 20 vs. 40 sessions) [25, 26]. The present finding that HBOT resulted in improved sleep quality is notable, as almost 75% of individuals with FM experience disturbed sleep, making it an important treatment target [27].

The results from the present study indicate that HBOT did not have a significant effect on fatigue in individuals with FM. These findings do not support results from two previous studies evaluating 60-session [17] and 20-session [25] protocols of HBOT, which showed improvements in energy levels and reduction in fatigue in individuals with FM. Fatigue has been associated with many other symptoms of FM, such as widespread pain,

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

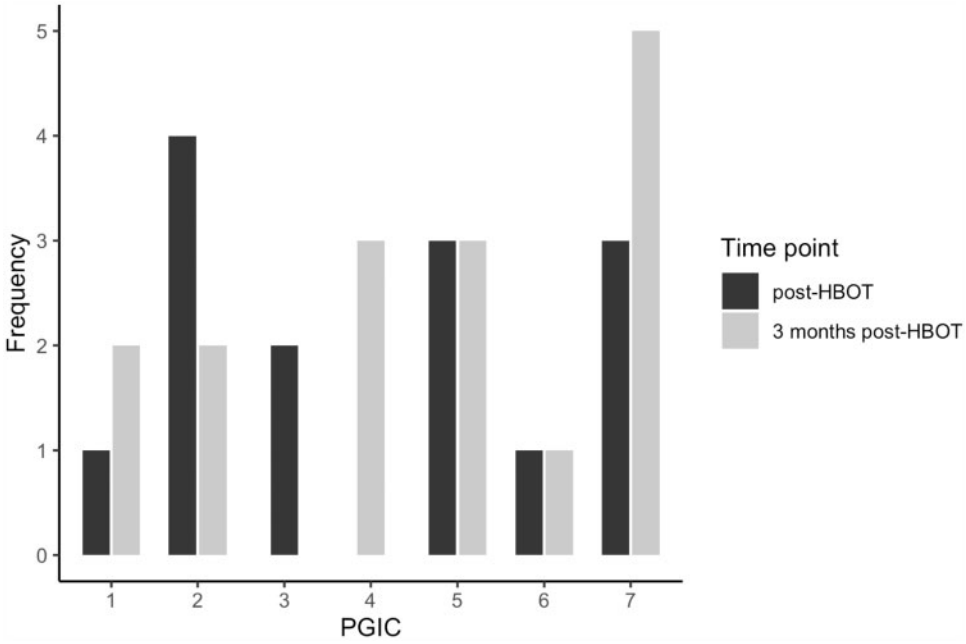

Figure 3. The PGIC assessment of combined group assessment after HBOT and at 3-month follow-up. *Denotes change from pre-HBOT ($P \leq 0.002$).

symptom severity, pain intensity, pain interference, cognitive impacts, catastrophizing, anxiety, and depressive symptoms [28], and is well recognized as a debilitating aspect of this disorder. In our trial the baseline fatigue VAS score for the WLC group was 43% of the baseline for the INT group. The lack of effect on fatigue in our study could be attributed to the baseline differences in our small sample size.

It is important to emphasize that the present study showed sustained improvements in functional impacts, psychological symptoms, and sleep at 3 months' follow-up after HBOT. Previously, one single cohort study evaluated the efficacy of HBOT for individuals with FM and interstitial cystitis at 6 months' follow-up after the intervention. The authors reported no improvement in pain, functional outcomes, or any measures related to interstitial cystitis [29].

Limitations

The present study has several limitations. First, the limited sample size was primarily geared to the assessment of feasibility and safety of HBOT in patients with FM. It also precluded us from making any definitive statements about the outcome measures that would need to be validated in a much larger, preferably multicenter, trial. Another study limitation is related to the duration and frequency of HBOT. The reported number of HBOT sessions varies from 20 to 60 sessions, with the duration from 1 to 2 hours, at 1.5–2.4 ATA. Ideally, dose–response HBOT studies would be conducted to definitively answer this question. Consequently, our results are limited to interpretation with the HBOT at 2.0 ATA for 90 minutes for 40 consecutive sessions over a period of 8 weeks. In research designs that incorporate a WLC group, the possibility exists that participants may alter their behavior during the control period of time, and this needs to be considered. The study was also limited by the exclusive use of self-reporting measures. Future studies may benefit from quantitative sensory testing of pain, sleep polysomnography, and other neurophysiological assessments of individuals with FM. Moreover, the lack of an active control group or sham controls may have also introduced a certain bias; however, the delayed-treatment control design that was used in the present study addressed most of the challenges related to the lack of controls. Finally, longer follow-up time intervals (e.g., 6 months, 1 year) after HBOT are needed to better understand the long-lasting benefits of this intervention for individuals with FM.

Conclusions

The results of this study indicate that HBOT is a safe and feasible intervention for patients with FM. Furthermore, the results suggest that HBOT has the potential to improve global function, symptoms of anxiety and depression, and sleep quality in individuals with FM. Our small sample size may have contributed to the lack of effect. This is the first study to report on the possible lasting benefits of HBOT on symptom improvement for individuals with FM, with maintenance of gains at 3 months after treatment, which is a significant clinical outcome for this population. These findings build on the current literature and provide further rationale for implementing HBOT as part of evidence-based pain management care for individuals with FM. Trials comparing the efficacy of

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022

HBOT with that of other therapeutic modalities should be the next step in defining the role of HBOT in the multidisciplinary care of patients with FM.

Acknowledgments

J. Katz is supported by a Canadian Institutes of Health Research Canada Research Chair in Health Psychology at York University.

H. Clarke is supported by a Merit Award from the Department of Anesthesiology and Pain Medicine at the University of Toronto.

References

1. McNally JD, Matheson DA, Bakowsky VS. The epidemiology of self-reported fibromyalgia in Canada. Chronic Dise Canada 2006;27(1):9–16.
2. Clauw DJ, Arnold LM, McCarberg BH, FibroCollaborative. The science of fibromyalgia. Mayo Clin Proc 2011;86(9):907–11.
3. Bernard AL, Prince A, Edsall P. Quality of life issues for fibromyalgia patients. Arthritis Care Res 2000;13(1):42–50.
4. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010;62(5):600–10.
5. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, The National Fibromyalgia Guideline Advisory Panel, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: Executive summary. Pain Res Manag 2013;18 (3):119–26.
6. Dinler M, Diracoglu D, Kasikcioglu E, et al. Effect of aerobic exercise training on oxygen uptake and kinetics in patients with fibromyalgia. Rheumatol Int 2009;30(2):281–4.
7. Katz DL, Greene L, Ali A, Faridi Z. The pain of fibromyalgia syndrome is due to muscle hypoperfusion induced by regional vasomotor dysregulation. Med Hypotheses 2007;69(3):517–25.
8. Valim V, Oliveira LM, Suda AL, et al. Peak oxygen uptake and ventilatory anaerobic threshold in fibromyalgia. J Rheumatol 2002;29(2):353–7.
9. Bardal EM, Olsen TV, Ettema G, Mork PJ. Metabolic rate, cardiac response, and aerobic capacity in fibromyalgia: A case-control study. Scand J Rheumatol 2013;42(5):417–20.
10. Shang Y, Gurley K, Symons B, et al. Noninvasive optical characterization of muscle blood flow, oxygenation, and metabolism in women with fibromyalgia. Arthritis Res Ther 2012;14(6):R236.
11. Mense S, Stahnke M. Responses in muscle afferent fibres of slow conduction velocity to contractions and ischaemia in the cat. J Physiol 1983;342(1):383–97.
12. Park JH, Phothimat P, Oates CT, Hernanz-Schulman M, Olsen NJ. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. Arthritis Rheum 1998;41(3):406–13.
13. Staples JR, Clement DB, Taunton JE, McKenzie DC. Effects of hyperbaric oxygen on a human model of injury. Am J Sports Med 1999;27(5):600–5.
14. El-Shewy KM, Kunbaz A, Gad MM, et al. Hyperbaric oxygen and aerobic exercise in the long-term treatment of fibromyalgia: A narrative review. Biomed Pharmacother 2019;109:629–38.
15. Yildiz S, Kiralp MZ, Akin A, et al. A new treatment modality for fibromyalgia syndrome: Hyperbaric oxygen therapy. J Int Med Res 2004;32(3):263–7.
16. Efrati S, Golan H, Bechor Y, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome—prospective clinical trial. PLoS One 2015;10(5):e0127012.
17. Hadanny A, Bechor Y, Catalogna M, et al. Hyperbaric oxygen therapy can induce neuroplasticity and significant clinical improvement in patients suffering from fibromyalgia with a history of childhood sexual abuse—randomized controlled trial. Front Psychol 2018;9:2495.
18. Bennett RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther 2009;11(4):R120.
19. Boomershine CS. A comprehensive evaluation of standardized assessment tools in the diagnosis of fibromyalgia and in the assessment of fibromyalgia severity. Pain Res Treat 2012;2012: 653714.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scand 1983;67(6):361–70.
21. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46(10):1121–3.
22. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol 1988;41(4):313–21.
23. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 2010;149(2):177–93.
24. Rampakakis E, Ste-Marie PA, Sampalis JS, et al. Real-life assessment of the validity of patient global impression of change in fibromyalgia. RMD Open 2015;1(1):e000146.
25. Atzeni F, Casale R, Alciati A, et al. Hyperbaric oxygen treatment of fibromyalgia: A prospective observational clinical study. Clin Exp Rheumatol 2019;37(suppl 116):63–9.
26. Guggino G, Schinocca C, Lo Pizzo M, et al. T helper 1 response is correlated with widespread pain, fatigue, sleeping disorders and the quality of life in patients with fibromyalgia and is modulated by hyperbaric oxygen therapy. Clin Exp Rheumatol 2019; 37(suppl 116):81–9.
27. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38(1):19–28.
28. Lukkahatai N, Walitt B, Espina A, Gelio A, Saligan LN. Understanding the association of fatigue with other symptoms of fibromyalgia: Development of a cluster model. Arthritis Care Res 2016;68(1):99–107.
29. Bosco G, Ostardo E, Rizzato A, et al. Clinical and morphological effects of hyperbaric oxygen therapy in patients with interstitial cystitis associated with fibromyalgia. BMC Urol 2019;19 (1):108.

Downloaded from https://academic.oup.com/painmedicine/article/22/6/1324/6140166 by guest on 05 December 2022