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Efficacy and safety of hyperbaric oxygen therapy for fibromyalgia: a systematic review and meta-analysis

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ABSTRACT

Objective To investigate the efficacy and safety of hyperbaric oxygen therapy (HBOT) for fibromyalgia (FM).

Design A systematic review and meta-analysis.

Data sources PubMed, EMBASE, Cochrane Library, Web of Science, VIP (China Science and Technology Journal Database), CNKI (China National Knowledge Infrastructure) and WanFang database were searched from from inception to 22 October 2022.

Eligibility criteria We included clinical trials (randomised controlled and non-randomised controlled trials) of HBOT for FM.

Data extraction and synthesis Two researchers independently screened the literature, extracted data and evaluated the quality of the included studies, with disagreements resolved by a third researcher. The Cochrane Collaboration checklists and the Methodological Index for Non-randomised Studies were used to assess the risk of bias. Meta-analysis was performed by RevMan V.5.4.1 software. Random effect models were used for meta-analysis.

Results Nine studies were included in this review, with a total of 288 patients. For pain assessment, we combined the results of the Visual Analogue Scale and Widespread Pain Index. The results showed that HBOT could relieve the pain of FM patients compared with the control intervention (standardised mean difference=−1.56, 95% CI (−2.18 to −0.93), $p<0.001$, $I^2=51\%$). Most included studies reported that HBOT ameliorated tender points, fatigue, multidimensional function, patient global and sleep disturbance in FM. Adverse events occurred in 44 of 185 patients (23.8%). Twelve patients (6.5%) withdrew because of adverse reactions. No serious adverse events or complications were observed.

Conclusions HBOT might have a positive effect in improving pain, tender points, fatigue, multidimensional function, patient global and sleep disturbance in FM, with reversible side effects. Low pressure (less than 2.0 atmospheric absolute) may be beneficial to reduce adverse events in FM. Further studies should be carried out to evaluate the optimal protocol of HBOT in FM.

PROSPERO registration number CRD42021282920.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Grading of Recommendations, Assessment, Development and Evaluations was used to assess the quality of evidence.
⇒ Rigorous methodology was used in this study, including explicit eligibility criteria, extensive database search, study selection by two reviewers working independently and risk of bias assessment.
⇒ Adverse events in hyperbaric oxygen therapy are negative outcomes that should be avoided, so it is important that we assess the risk of such effects to better understand the appropriate protocol regarding hyperbaric oxygen therapy.
⇒ The small number of randomised controlled trials included in the studies may lead to an overall risk of bias or insufficient evidence.

INTRODUCTION

Fibromyalgia (FM) is an incurable common syndrome with unclear origin.[1] It is characterised by chronic pain at multiple tender points lasting for more than 3 months and is usually accompanied by clinical manifestations such as fatigue, sleep disturbance, cognitive dysfunction and depressive symptoms.[2 3] It is estimated that 2%–8% of the population is affected by FM worldwide.[4] FM is more frequent in females, with a female-to-male ratio of 9:1.[5]

The cause of FM syndrome is not yet fully understood, while the symptoms may be induced by infection, diabetes, rheumatic diseases, traumatic brain injury or mental trauma.[4 6] Certain studies have reported a history of childhood sexual abuse in some patients with FM.[7 8] Currently, treatment options mainly include pharmacological therapies, physical exercise, meditative exercise therapy and behavioural therapy.[9–12] However, these methods only temporarily or moderately alleviate pain symptoms and often produce unbearable adverse effects that interfere with the patient's quality of life and reduce their compliance.[13] Therefore, there is a need for new and effective chronic pain treatments that can be tolerated by patients without significant adverse effects.

Accumulating evidence suggests that hyperbaric oxygen therapy (HBOT) is a non-invasive modality with lasting efficacy

to treat FM.[14–17] HBOT is conducted by intermittently breathing 100% oxygen in a pressure chamber above one atmospheric absolute pressure (ATA). HBOT can raise the partial pressure of oxygen in alveoli, leading to a favourable increase in dissolved oxygen in plasma.[18] The increase in pressure and oxygen causes more dissolved oxygen to be delivered to the tissue through the blood, which oxygenates the ischaemic tissue.[19] HBOT has shown strong anti-inflammatory potential by reducing the activation of glial cells and inflammatory mediators so that it could relieve pain under different chronic pain conditions.[14] The anti-inflammatory effects of HBOT also correct associated abnormal brain activities and glial function, which may benefit FM patients.[20] The increase in oxygen concentration caused by HBOT has been shown to improve the mitochondrial dysfunction of FM patients, leading to changes in brain metabolism and glial function, and may reduce the abnormal brain activities associated with FM.[20] Although some studies have reported a positive effect of HBOT on FM, HBOT has not been recommended by guidelines as a complementary treatment for FM due to the lack of sufficient evidence.[21 22]

Mascarenhas *et al*[23] proposed that HBOT for the management of FM was moderate evidence in a systematic review. However, only two studies on HBOT for FM were included, and there was no meta-analysis. In addition, only two outcome measures (pain and quality of life) were investigated. To better understand the overall efficacy and safety of HBOT for FM, we conducted a systematic review and meta-analysis with more studies to investigate HBOT in the treatment of the inner Core Outcome Set of FM symptoms (pain, tenderness, fatigue, multidimensional function, patient global, sleep disturbance)[24] and estimate its safety.

METHODS

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25] The protocol for this study is available online (PROSPERO trial registration number: CRD42021282920).

Search strategy

A literature search was conducted to identify all articles involving the use of hyperbaric oxygen to treat FM. The search strategy is shown in online supplemental Appendix 1. PubMed, EMBASE, Web of Science, Cochrane Library, VIP (China Science and Technology Journal Database), CNKI (China National Knowledge Infrastructure) and WanFang database were searched from from inception to 22 October 2022. The search included MeSH and free text terms such as “hyperbaric oxygen therapy”, “fibromyalgia” and synonyms.

Inclusion and exclusion criteria

We considered including all available information for systematic review due to the lack of data on this disease and the suspected lack of randomised controlled trials (RCTs). The criteria for inclusion were as follows: (1) study design: RCTs and non-RCTs; (2) subjects: FM patients conformed to the 2016 American College of Rheumatology (ACR) diagnostic criteria[26] (ie, They met the following criteria: generalised pain for at least 3 months and a Widespread Pain Index (WPI) ≥7 and symptom severity scale (SSS) ≥5 or a WPI of 4–6 and an SSS score ≥9); (3) the intervention: patients in the experimental group received HBOT as the intervention measure, and patients in the control group received conventional treatment or nothing. The conventional treatment was any pharmacological or nonpharmacological therapy other than HBOT. The course of treatment and parameters were unlimited. (4) Outcome indicators: the inner Core Outcome Set of FM symptoms (pain, tenderness, fatigue, multidimensional function, patient global, sleep disturbance) and adverse events (AEs). The exclusion criteria were as follows: animal studies, reviews, duplicate publications, irrelevant studies, editorial materials, patients, case reports or meeting abstracts.

Literature screening and data collection

Two reviewers (JY and HM) independently assessed the eligibility of each article. Duplicate articles were eliminated. Irrelevant articles were excluded by reading the title and abstract, and then the full text was read to further screen out articles that met the inclusion criteria. Articles without full text or data were excluded after three or more attempts to email the lead author and obtain no response. The decision to include each article was made independently according to the inclusion criteria, with disagreements resolved by a third reviewer (XC). Reviewers followed PRISMA criteria for systematic evaluation.

A predesigned form was used for information extraction. The content included the article’s basic information (author, year of publication, title); research types; patient demographics (age, gender); intervention and control measures (duration, frequency, sessions, follow-up); outcome indicators; the data of results and indicators that reflected research quality. Data collection was completed independently by two researchers (JY and HM) and checked with each other. In case of disagreement, a third researcher (XC) assisted in resolving the disagreement.

Types of outcome measures

The inner Core Outcome Set of FM symptoms suggested by Mease *et al*[24] can be quantitatively or qualitatively analysed. The primary outcome measure was pain, and the secondary outcome measures included tenderness, fatigue, multidimensional function, patient global, sleep disturbance and AEs.

Pain and tenderness

Assessment methods included the Pain Visual Analogue Scale (VAS), number of tender points, pain threshold and WPI.

Multidimensional function

Assessment methods included the Fibromyalgia Impact Questionnaire (FIQ) and 36-Item Short Form Survey (SF-36).

Fatigue

Assessment methods of fatigue included the Fatigue Severity Scale, Functional Assessment of Chronic Illness Therapy Fatigue scale, Fatigue VAS and CR-10 Borg Scale.

Patient global

The Patient Global Impression of Change (PGIC) was used to assess this outcome measure.

Sleep disturbance

Assessment methods included the Jenkins Sleep Scale and Pittsburgh Sleep Quality Index.

Adverse events

This indicator included AEs, withdrawals due to AEs, and complications.

Risk of bias assessment

Reviewers assessed the quality of the included articles using the Cochrane Collaboration checklists[27] for 3 RCTs and the Methodological Index for Non-randomised Studies (MINORS)[28] for 6 non-RCTs. The Cochrane checklists assessed selection bias, implementation bias, measurement bias, attrition bias, reporting bias and other bias. In the Cochrane ROB tool, the risk of bias was classified as 'low risk', 'unclear' and ' high risk'. Review Manager version V.5.4.1 was used to generate the risk of bias graph of the three RCTs. The MINORS checklists included twelve items (0–24 scores) for comparative studies and eight items (0–16 scores) for non-comparative studies. The score for each item was 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). Comparative studies scoring >19 or non-comparative studies scoring >12 were considered high quality. The quality of the included studies was assessed independently by two reviewers (JY and HM). Again, any controversy in the assessment was resolved through discussion with a third reviewer (XC).

Statistical analysis

RevMan V.5.4.1 software provided by the Cochrane Collaboration was used to conduct a meta-analysis. The standardised mean difference (SMD) and its 95% confidence intervals (CI) were used as the analysis statistics because across studies different rating tools are used to measure the same outcome.[29] Forest plot tests were conducted, and meta-regression analysis was used to test heterogeneity. The χ^2 test was used to analyse whether there was statistical heterogeneity among the results of each study. This study used the random effects model for meta-analysis because the random effects meta-analysis allowed for differences (treatment areas, concomitant treatments and HBOT regimen) in treatment effects among different studies.[30]

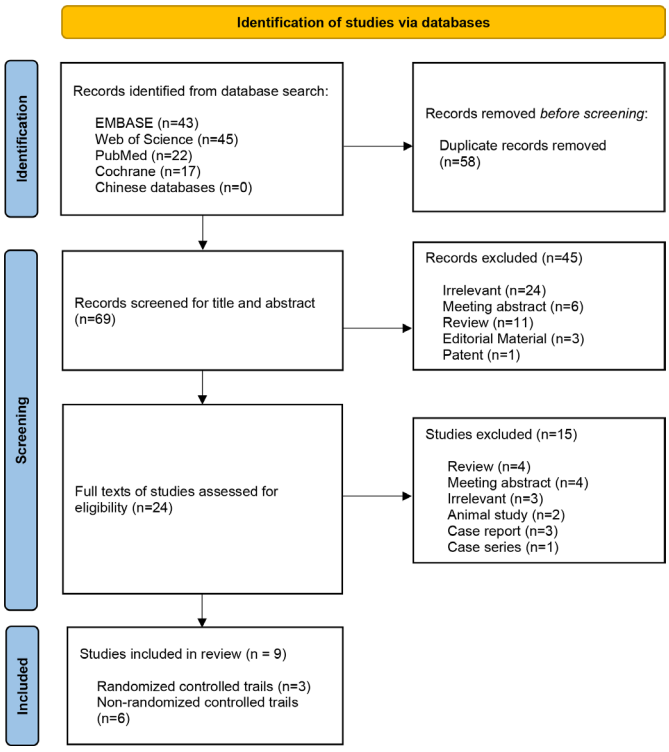

Figure 1 PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Grade the quality of evidence

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to grade the quality of the evidence.[31] The risk of bias, inconsistency, indirectness, imprecision and publication bias were assessed. The quality of evidence was rated 'high', 'moderate', 'low' or 'very low'.

Patient and public involvement

Patients and the public were not involved in this study.

RESULTS

Characteristics of the included studies

A total of 69 eligible articles were obtained by a literature search. After screening, nine studies (three RCTs and six non-RCTs) met the inclusion criteria.[32–40] The flow diagram is shown in figure 1. A total of 288 patients were included in this study. Table 1 shows the characteristics of the included articles.

Quality assessment

Figure 2 shows the risk of bias graph of the three RCTs according to the Cochrane ROB tool. Of the RCTs included, studies by Yildiz *et al*[40] and Hadanny *et al*[38] had an unclear risk of selection bias because of the lack of specific randomisation methods and no indication of allocation concealment. All RCTs were judged to have an unclear or high risk of performance bias because researchers did not adopt blinding. All RCTs were at low risk for detection bias and attrition bias. However, the risk of reporting bias and other bias in all RCTs were

Table 1 Characteristics of the included articles

Author, year	Patients (N)		Intervention (HBOT)		Comparison	Outcome measures	Adverse events and the no of patients		Study design
	Intervention	Control	Protocol	Sessions/ length			Adverse events	Patients (N)	
Yildiz 2004[40]	26	24	90 min, 2.4ATA, 5d/w	15/3 weeks	90 min, 1ATA, 5d/w	Number of tender points, Pain threshold, Pain VAS	–	–	RCT
Hadanny 2018[38]	15	15	90 min, 2ATA, 5d/w	60/12 weeks	Psychotherapy	WPI, FIQ, SF-36	Mild barotrauma	12	RCT
							Headache	1	
Izquierdo-Alventosa 2020[33]	17	16	90 min, 1.45ATA, 5d/w	40/8 weeks	Conventional therapy	VAS, Pain threshold, CR-10 Borg scale	–	–	RCT
Efrati 2015[39]	27	26	90 min, 2ATA, 5d/w	40/8 weeks	No treatment	Number of tender points, Pain threshold, FIQ, SF-36	Mild barotrauma	13	NCT
							Dizziness, claustrophobia and inability to adjust ear pressure by “ear pumping”	5	
Guggino 2020[34]	22	14	90 min, 2ATA, 5d/w	40/8 weeks	No treatment	Number of tender points, Pain VAS, Fatigue VAS, WPI, FACIT fatigue, PSQI	–	–	NCT
Curtis 2021[32]	9	8	90 min, 2ATA, 5d/w	40/8 weeks	Conventional therapy	FIQR, FSS, JSS, PGIC, Fatigue VAS	Mild middle-ear barotrauma	3	NCT
							New-onset myopia	4	
Casale 201[35]	25	–	91 min, 2.4ATA	20/4 weeks	–	Neuromuscular efficiency	Side effects	2	NCT
Bosco 2019[36]	12	–	90 min, 2ATA, 5d/w	20/4 weeks	–	WPI	–	–	NCT
Atzeni 2019[37]	32	–	90 min, 2.5ATA, 3d/w	20/4 weeks	–	Pain VAS, FACIT, PSQI, FIQR, SF-36	Mild, reversible middle ear barotrauma	2	NCT
							Dizziness	1	
							Claustrophobia	1	

ATA, atmospheric absolute pressure; d/w, days/week; FACIT fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FIQ, Fibromyalgia Impact Questionnaire; FIQR, Revised FIQ; FSS, Fatigue Severity Scale; JSS, Jenkins Sleep Scale; NCT, non-randomised controlled trial; PGIC, Patient Global Impression of Change; PSQI, Pittsburgh Sleep Quality Index; RCT, randomised controlled trial; SF-36, 36-Item Short Form Survey; VAS, Visual Analogue Scale; WPI, Widespread Pain Index.

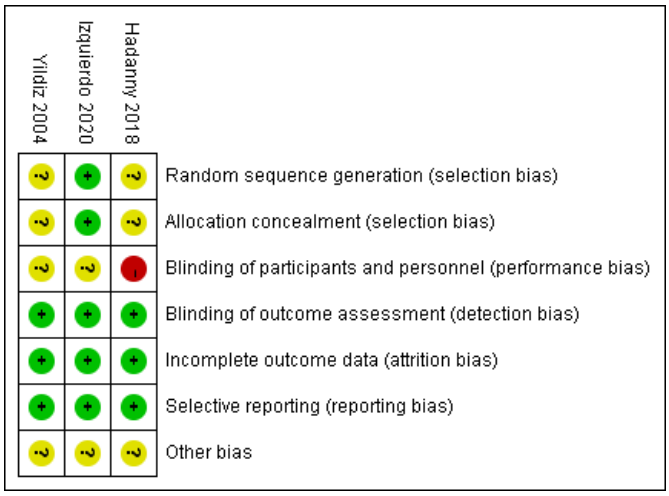

Figure 2 Risk of bias graph for the included randomised controlled trials across five domains. The red circle indicates a high risk of bias within that domain for a given study, the yellow circles indicate an unclear risk of bias and the green circles indicate a low risk of bias.

unclear, mainly due to the lack of follow-up. Table 2 shows the quality assessment of the six non-RCTs. The average MINORS scores for non-comparative and comparative studies were 9.7 and 19.7, respectively. Studies by Efrati *et al*[39] and Curtis *et al*[32] were considered high quality. In non-RCTs, lack of bias assessment, study size calculation and follow-up were the most common reasons for low MINORS scores.

Efficacy of HBOT

Because of the small number of studies, insufficient data that could be pooled and heterogeneity among different study types, only pain relief from three RCTs was included in the meta-analysis, and the other outcome indicators were only analysed descriptively.

Pain relief

Seven studies (three RCTs and four non-RCTs)[33 34 36–40] reported that HBOT alleviated the pain level of FM, as documented by the decrease in rating scales related to pain. We conducted a meta-analysis on pain relief of three RCTs.[33 38 40] For pain assessment, we combined the results of VAS and WPI. Meta-analysis of a random effect model showed that the pain relief in the HBOT group was better than that in the control group (SMD=−1.56, 95% CI (−2.18 to −0.93), $p<0.001$, $I^2=51\%$) (figure 3).

Tenderness

Three studies[34 39 40] reported that HBOT reduced the number of tender points in FM. Jeschonneck *et al*[41] found that vasoconstriction in patients with FM occurred in the skin above the tender point. This confirmed that FM syndrome was associated with local hypoxia of the skin covering the tender points. Lund *et al*[42] proposed that in FM with primary aetiology, muscle oxygenation was abnormal or low, at least in the muscle trigger point region, as recorded by oxygen multipoint electrodes on the muscle surface. HBOT could break the vicious cycle of pain-hypoxia because it increased the pain threshold to reduce the number of tender points in patients with FM.[40]

Multidimensional function

Three studies[32 38 39] reported that HBOT improved FM-related functional impairment and overall symptoms, as documented by the decreased score of the FIQ or FIQ-R questionnaire. These studies may support the use of HBOT to reduce the effects of FM on global symptoms and functional activities. Studies by Hadanny *et al*,[38] Efrati *et al*[39] and Atzeni *et al*[37] reported the SF-36, which was used to assess the quality of life. All three studies showed that HBOT could effectively improve the quality of life of FM. In addition, Hadanny *et al*[38] had shown that

Table 2 Quality assessment of the included non-randomised controlled trials using the Methodological Index for Non-randomised Studies

Assessment	Efrati 2015 *et al*[39]	Guggino *et al* 2020[34]	Curtis *et al* 2021[32]	Casal *et al* 2019[35]	Bosco *et al* 2019[36]	Atzeni *et al* 2019[37]
1. A clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	2	0	1	1	0	0
6. Follow-up period appropriate to the aim of the study	0	0	2	0	2	0
7. Lost to follow-up less than 5%	0	0	2	0	0	0
8. Prospective calculation of the study size	2	2	0	0	0	2
9. An adequate control group	2	2	2	–	–	–
10. Contemporary groups	2	2	2	–	–	–
11. Baseline equivalence of groups	2	2	2	–	–	–
12. Adequate statistical analyses	2	2	2	–	–	–
Total score	20	18	21	9	10	10

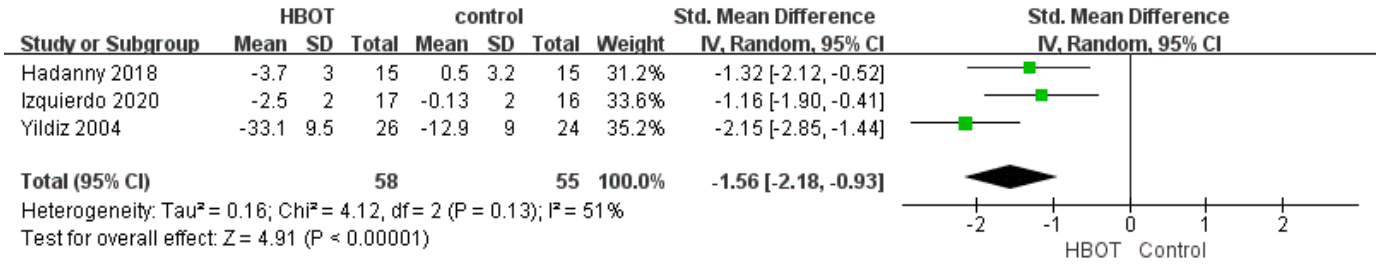

Figure 3 Forest plot of pain relief. HBOT, hyperbaric oxygen therapy.

improvements in quality of life with FM were associated with improvements in brain performance parameters seen in brain function (single-photon emission computerized tomography) and structure (magnetic resonance imaging-diffusion tensor imaging). This may be because HBOT can improve brain function and microstructure by inducing neural plasticity in humans.[43 44]

Fatigue

Three studies[33 34 37] showed that HBOT could reduce fatigue in FM patients, while Curtis *et al*[32] reported that HBOT had no significant effect on fatigue in FM. Studies have shown that HBOT reduced fatigue in chronic fatigue syndrome,[45] which was attributed to its ability to reduce reactive oxygen species and acid-lactic acid levels, as well as muscle fatigue after exercise.[46] HBOT alleviated fatigue in FM patients, possibly because HBOT increased oxygen supply to the musculoskeletal system, thereby activating cellular activity and promoting the metabolism of fatigue-related substances.[47] Clinical studies have shown that increased plasma proinflammatory cytokine levels trigger symptoms such as fatigue, fever, sleep, pain and myalgia in FM patients.[48] HBOT can improve FM symptoms by reducing the upregulation of proinflammatory cytokines in FM. Atzen *et al*[37] proposed that the fatigue of FM was only improved after 20 treatments, indicating that the number of treatments would affect the efficacy of HBOT. In Curtis *et al*'s study,[32] the lack of an effect of HBOT on fatigue may be attributed to baseline differences in the small sample size. In addition, Casale *et al*[35] found that HBO did not directly increase FM muscle strength or alter muscle fibre content to alleviate fatigue but increased the ability of the central motor command to generate the same effort with fewer recruited fibres.

Patient global

Only one study[32] reported PGIC, which assessed global response to treatment and has been associated with clinical symptoms in patients with FM. Curtis[32] reported that patients with FM had a different degree of symptom improvement after HBOT and at a 3-month follow-up. After HBOT treatment, 'almost the same' was the most common impression of global symptoms in FM patients (44.4%). However, at the 3-month follow-up, 'a great deal better' was the most common impression of global symptoms in FM patients (41.7%). This showed that HBOT may be effective for a long time.

Sleep disturbance

Three studies reported sleep quality. Guggino *et al*[34] reported that HBOT did not improve the total sleep time of FM patients but improved their sleep quality. Curtis *et al*[32] proposed that HBOT improved sustained sleep quality in FM at a 3-month follow-up assessment. However, Atzeni *et al*[37] indicated that HBOT did not significantly improve the sleep quality of FM. This inconsistency may be related to the different number of HBOT sessions, which needs further study.

AEs of HBOT

Five studies reported the side effects of HBOT for FM (as shown in table 1). AEs occurred in 44 of 185 patients (23.8%). Twelve patients (6.5%) withdrew because they could not tolerate adverse reactions. Of these AEs, there were 30 cases of mild barotrauma, 4 cases of new-onset myopia, 1 case of headache, 7 cases of dizziness, claustrophobia, inability to adjust ear pressure by 'ear pumping' and 2 cases of side effects (not clearly reported). The predominant AE was mild barotrauma that could be resolved spontaneously and did not prevent patients from completing the treatment regimen. No serious side effects, complications or deaths were reported.

Grade analysis of the evidence

The quality of pain relief was 'moderate'. Although there was a serious risk of bias and inconsistency, there was no serious directness or imprecision. In addition, the outcome of pain relief has a large effect. The GRADE evidence profile is shown in table 3.

DISCUSSION

In this study, we focused on the efficacy of HBOT on the inner core outcomes of FM. Pain relief was the primary outcome and could be meta-analysed (three RCTs). Tenderness, fatigue, multidimensional function, patient global, sleep disturbance and AEs were secondary outcome measures and were analysed descriptively because of the limited number of studies or limited available data that could be combined. After a systematic review, we found that HBOT could relieve the pain of FM patients compared with the control intervention (SMD=−1.56, 95% CI (−2.18 to −0.93), $p<0.001$, $I^2=51\%$). In addition, most of the included studies have shown that HBOT could significantly improve tender points, fatigue, quality

Table 3 GRADE evidence profile

Outcome	Certainty assessment					Effect			Certainty
	Risk of bias	Inconsistency	Directness	Imprecision	Others	Number of studies	Number of individuals	Rate (95% CI)	
Pain relief	Serious*	Serious†	Not serious‡	Not Serious§	Large effect¶	Three RCTs	113	SMD: −1.56 (−2.18 to −0.93)	⊗⊗⊗○ Moderate

*Most of the included studies were assessed as some concerns/high-risk bias.
†I^2 >50%.
‡Direct participants, intervention and outcomes.
§Total sample size >100.
¶SMD >0.8.
GRADE, Grading of Recommendations, Assessment, Development and Evaluations; SMD, standardised mean difference.

of life, patient global and sleep disturbance in patients with FM. However, Curtis *et al*[32] found that HBOT had no positive effect on fatigue reduction of FM, and Atzeni *et al*[37] indicated that HBOT did not significantly improve the quality of life of FM. This inconsistency might be due to baseline differences in small sample sizes or the insufficient number of HBOT sessions. Of the 185 patients with FM who received HBOT, 44 patients had adverse reactions during HBOT treatment (23.8%) and 12 patients withdrew (6.5%) because they could not tolerate the side effects. However, in one retrospective study of 1.5 million cases of treatment with HBOT, the AE rate was only 0.68%.[49] We speculated that patients with FM might have a lower pain threshold and may be more sensitive to discomfort than patients with other diseases. Mild barotrauma was the most common complication of HBOT for FM. Patients may experience pressure, difficulty in ear balance, earache and discomfort during compression.[50] However, mild barotrauma can be resolved spontaneously and does not prevent patients from completing the treatment, and can usually be prevented by appropriate screening.[51] Oliaei *et al*[52] found that most complications of HBOT occurred when the pressure applied exceeded 2.0 ATA. The articles included in this study mostly used hyperbaric oxygen chambers of 2–2.5 ATA for the treatment of FM, which may lead to side effects. A randomised controlled study[33] confirmed that low-pressure HBOT (1.45 ATA) was effective in the treatment of FM without AEs. Therefore, a pressure lower than 2.0 ATA may be a good choice for patients with FM to avoid side effects. Further studies are needed to explore the efficacy and safety of low-pressure HBOT for FM. In addition, contraindications for HBOT should be strictly screened before treatment, and the appropriate pressure and duration of treatment should be determined according to the patient's tolerance.

Patients with FM in the control group received conventional treatment or nothing in the included studies. Yildiz *et al*,[40] Efrati *et al*[39] and Guggino *et al*[34] did not give any treatment to the patients in the control group, while Hadanny *et al*,[38] Izquierdo-Alventosa *et al*[33] and Curtis *et al*[32] performed conventional treatment for the patients in the control group. The conventional treatment that FM received included psychotherapy, medications, physical activity, nutrition therapy, massage, acupuncture, behavioural therapy, and cognitive therapy. Therefore, HBOT may be effective both as an adjunctive therapy and as an independent treatment. Most of the included studies used the same HBOT protocol, which was 100% oxygen at 2–2.5 ATA, 90 min per session, 5 days per week. Only a study by Izquierdo-Alventosa *et al*[33] used 1.45 ATA to avoid the side effects of HBOT. The length of treatment in the included studies ranged from three to twelve weeks, of which the study by Yildiz *et al*[40] lasted 3 weeks, the study by Hadanny *et al*[38] lasted 12 weeks, three non-comparative studies[35–37] lasted 4 weeks and the rest of the studies lasted 8 weeks. A rodent study found that the anti-injury effects of HBOT were apparent immediately after treatment and lasted for up to 5 hours.[19] In a rat neuropathic pain model, 2 weeks of HBOT resulted in a significant improvement in pain levels during and after treatment.[53] Atzeni *et al*[37] proposed that 2–4 weeks of HBOT treatment significantly improved pain and anxiety symptoms in FM, while fatigue only improved after 4 weeks. In addition, sleep quality and depressive symptoms were not positively affected in FM after 4 weeks of HBOT. In this review, only Curtis *et al*[32] mentioned a follow-up measurement (3 months) and found that HBOT can continuously improve patient global, psychological symptoms and sleep quality in FM. Another study[16] showed that HBOT for 10 days had a rapid onset, dose-dependent and long-lasting analgesic effect in patients with idiopathic trigeminal neuralgia documented a reduction in the dosage of carbamazepine analgesics and lower pain VAS. Therefore, long-term treatment with HBOT may be beneficial to improve symptoms of FM or prolong efficacy. However, the prolonged treatment window of patients is likely to cause side effects. Studies have shown that human lenses exposed to 2.0–2.5 ATA and 100% oxygen for 90 min once a day will lead to the development of myopia and cataracts after 150–850 courses of HBOT.[54] However, when exposed to 2.5 ATA and 100% oxygen for 90 min once a day for 48 courses, the above side effects rarely occur.[55] It is challenging to establish the effect and optimal dose–response curves of HBOT in FM considering both safety and efficacy.

There is growing evidence that HBOT is a non-invasive way to treat chronic pain diseases with long-lasting efficacy and minor adverse effects.[13] In murine models of pain, HBOT has been shown to inhibit pain sensation, which may be due to the nitric oxide-dependent release

of opiate peptides and could be restrained by an antagonist, naltrexone.[56 57] This effect works in the central system but also involves HBO activating μ-opioid and K-opioid receptors in the spinal cord and releasing neuronal dynorphins.[58] In murine models of arthritis, HBOT has also been shown to affect inflammatory pain by reducing mechanical hypersensitivity and inflammation.[59] Patients with FM often experience degenerative changes in muscle, abnormal oxygen pressure and lower muscle blood flow due to hypoxia.[16 60] Local ischaemia causes mitochondria to produce higher levels of free radicals to induce apoptosis, reduce ATP synthesis and increase lactate concentration in the muscle, thus ultimately leading to muscle weakness and pain.[61 62] HBOT improves muscle oxygenation in FM, which can reduce the tissue lactate concentration and help maintain ATP levels, thus possibly preventing tissue damage in ischaemic tissue.[63] It raises the oxygen concentration in all tissues far above physiological levels to cause hyperoxia, which breaks the hypoxic-pain cycle in patients with FM.[63] In addition, the high excitability of pain processing pathways in the brain and low activity of pain inhibition pathways may cause excessive pain in FM.[64] Studies have shown that patients with FM have higher activity in the somatosensory cortex and lower activity in the frontal, medial frontal, cingulate gyrus and cerebellar cortex than healthy subjects.[65] HBOT has been shown to increase neurotrophic and nitric oxide levels, reduce oxidative stress, promote cell metabolism by enhancing the mitochondrial function of neurons and glial cells, and may even promote the production of endogenous neural stem cells.[66] The specific mechanism of HBOT on FM needs to be further investigated.

The quality of evidence (pain relief of HBOT for FM) assessed using the GRADE system was moderate. There are inherently ethical and logistical difficulties in handling sham control in HBOT experiments. In two RCTs,[33 38] the researchers did not use the sham control/placebo in the control group, which may lower the quality of the evidence. The heterogeneity of the outcome may be caused by the population and HBOT regimen. However, the large effect (SMD >0.8) may increase the quality of the evidence. Therefore, we have a moderate degree of confidence in our estimated effect. The true value may be close to the estimated value, but there is still a chance that they could be very different.

There are some limitations in this systematic review. The main limitation is that the small number of RCTs included may lead to an overall risk of bias or insufficient evidence. Second, HBOT protocols (the length of treatment and pressure parameters) have clinical heterogeneity, which may introduce bias to the results. Third, we only retrieved data from Chinese and English databases, which may limit the data availability or cause language bias. Finally, due to the small number of included studies and heterogeneity, we did not conduct a subgroup analysis. Therefore, we cannot evaluate the efficacy of different HBOT regimens.

In conclusion, this study shows that HBOT may have a good effect in improving pain, tender points, fatigue, multidimensional function, patient global and sleep disturbance in FM, with reversible side effects. Low pressure (less than 2.0 ATA) may be beneficial to reduce AEs in patients with FM. Further high-quality and large-sample RCTs should be carried out to further evaluate its efficacy and safety.

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