ABSTRACT

Introduction Fibromyalgia (FM) is an unexplained chronic condition characterised by generalised pain, sleep disturbances, autonomic disturbances, anxiety, fatigue and cognitive impairment. FM is a prevalent chronic disease worldwide that imposes a significant burden on individuals and society. Emerging evidence suggests that environmental interventions, such as exposure to hyperbaric oxygen therapy (HBOT), can relieve pain and improve the quality of life in patients with FM. This study will systematically and comprehensively assess the effectiveness and safety of HBOT in patients with FM and provide evidence to support its implementation. We hope that the final review will be helpful in supporting the decision-making processes related to treatment programmes.

Methods and analysis This protocol is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols guidelines. Ten key databases, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE (Excerpt Medica Database), PsycINFO, CINAHL (Cumulative Index to Nursing and Allied Health Literature), PEDro, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, WANFANG and VIP (Chinese Scientific Journal Database), will be searched from inception through December 2022 to identify relevant randomised controlled trials examining the effectiveness of HBOT in patients with FM published in English or Chinese. Two reviewers will independently complete the study screening, selection, and data extraction and assess the risk of bias in the included studies using the 0–10 PEDro Scale. Narrative or quantitative syntheses will be performed and a systematic review and meta-analysis will be performed using Review Manager V.5.3 statistical software.

Ethics and dissemination Ethical approval was not required for this protocol. The results of the final review will be disseminated in a peer-reviewed journal.

PROSPERO registration number CRD42022363672

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol is reported per the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA-P) guidelines, and the final review will be conducted per the guidelines of the Cochrane Handbook and PRISMA.

⇒ The following 10 key databases will be searched: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO, CINAHL, PEDro, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, WANFANG and VIP.

⇒ Two reviewers will independently complete the study screening, selection, and data extraction and assess the risk of bias of the included studies using the 0–10 PEDro Scale, and possible disagreements will be resolved through discussion or negotiation with a third author.

⇒ To reduce the degree of heterogeneity in the study, we developed relatively strict inclusion criteria and, if applicable, prespecified subgroup analyses will be conducted.

⇒ The number of randomised controlled trials may be limited, which could lead to conclusions with relatively weak generalisability.

INTRODUCTION

Fibromyalgia (FM) is an unexplained chronic condition characterised by generalised pain, sleep disturbances, autonomic disturbances, anxiety, fatigue and cognitive impairment. As one of the most common causes of chronic pain, it has become a major concern for the National Health Service, with a 2%–4% prevalence worldwide. FM has become the third most common musculoskeletal disorder, after low back pain and osteoarthritis. The incidence ratio of FM in men and women is approximately 1:9 worldwide. The incidence rate is proportional to age, with the highest incidence in the 50–60 years age group. FM seriously affects the quality of life of patients and the labour force, causing about 50% of patients to have difficulty conducting daily tasks and 30%–40% to be unable to continue to work. Furthermore, it significantly increases society’s economic burden and results in a fivefold increase in healthcare spending.

As one of the most common musculoskeletal disorders of unknown cause, FM is characterised by chronic generalised skeletal muscle pain. Because different manifestations and individual differences in dominant...
symptoms exist, the pathogenesis of FM has not been fully elucidated. The current relevant evidence shows that the central, peripheral and autonomic nervous systems, immune system, neuroendocrine secretion, and psychological and social stress may be the factors causing its pathogenesis. Meanwhile, recent studies indicated the association between vitamin D deficiency and FM, and generally, patients with FM are accompanied by vitamin D deficiency. Related studies have demonstrated that hypoxia is the cause of hyperventilation, and respiratory alkalosis caused by hyperventilation leads to endocrine disorders and impairs vitamin D production, which may also cause FM. Furthermore, recent studies have found that patients with FM have lower capillary density and lower mean oxygen pressure, so it is believed that local hypoxia is one of the causes of muscle degeneration in patients with FM.

Patients with FM should follow the principle of individualisation step by step, adopt multidisciplinary comprehensive rehabilitation treatment and pay more attention to the special condition of the patient. Guidelines and recommendations indicate that non-pharmacological therapy is the primary mode of treatment. Appropriate non-pharmacological therapies include exercise therapy, physical therapy, behaviour therapy and psychotherapy. Furthermore, exercise therapy, including aerobic exercise and muscle-strengthening exercises, is considered the most appropriate non-pharmacological treatment. Pharmacological therapy is only considered when patients have severe pain or sleep disturbances. Moreover, relevant research results show that antidepressants and central nervous system inhibitors have little effect on reducing pain and improving quality of life. Meanwhile, pharmacological therapy usually leads to headache, nausea, fatigue, lethargy and other adverse reactions, resulting in poor patient compliance. Many non-pharmacological therapies have been explored, and hyperbaric oxygen therapy (HBOT), a non-invasive and non-pharmacological approach, is evoking interest.

According to the Undersea and Hyperbaric Medical Society, HBOT is a treatment where the patient breathes 100% oxygen in a hyperbaric oxygen chamber at sea level pressure (1 atmosphere absolute (ATA), 1 ATA=760 mm Hg). The oxygen chamber pressure and treatment duration are determined according to the patient’s condition. Treatment for adults usually requires pressurisation to 2.0–3.0 ATA for 60–120 min once or twice a day; however, for infants or patients with serious underlying diseases and unstable vital signs, treatment usually requires pressurisation to 1.5–1.8 ATA. As a reliable treatment, HBOT is widely used to treat various diseases, including decompression sickness, carbon monoxide poisoning, femoral head necrosis, skin grafts and flaps, radiation-induced injuries, diabetic foot, among others. During the treatment period, patients typically have arterial partial pressures of oxygen greater than 2000 mm Hg and tissue partial pressures of oxygen between 200 mm Hg and 400 mm Hg. The dissolved oxygen in plasma can be increased from 0.5 ml/dL to 6 mL/dL at 3 ATA.

With the continuous development of technology, HBOT has proven to be a highly effective and safe method to treat various diseases. Most side effects observed during treatments are mild and reversible, with the most common side effect being middle ear barotrauma, which occurs when the patient’s middle ear pressure is not equalised. Studies have confirmed the positive effect of HBOT in the treatment of different types of pain, such as complex regional pain syndrome and migraine. Moreover, there is a growing body of evidence to suggest that the mechanisms of HBOT on FM may include enhancing the production of reactive oxygen species (ROS) and reactive nitrogen species, promoting cell growth, and regulating the inflammatory response. It is widely known that ROS plays a key role in promoting new angiogenesis and increasing blood flow. Studies concerning patients with FM have shown that pain worsens as nitric oxide levels increase. When blood circulation is blocked in patients with FM, ATP decreases and lactic acid increases, which is also responsible for pain aggravation. It is worth noting that HBOT plays a positive role in reducing nitric oxide (NO) content. HBOT can improve oxygen transport in tissues, reduce lactic acid accumulation and increase tissue oxygen concentration.

Additionally, HBOT can increase cerebrovascular flow, promote the integrity of the blood-brain barrier, and reduce inflammation, which may also be a cause for relief in patients with FM. It has been reported that HBOT can correct abnormal brain activity in pain-related areas while effectively alleviating FM symptoms and improving the quality of life. Barilario et al showed that HBOT could reduce brain activity in the posterior cortex and increase activity in the cerebellar cortex, cingulate and medial temporal regions, with beneficial effects on already damaged brain regions.

In recent years, there has been increasing interest in the application of HBOT for treating patients with FM; however, the results of clinical trials have been inconsistent. For example, Hadanny et al and Atzeni et al reported that HBOT reduced fatigue in patients with FM. In contrast, Curtis et al showed that HBOT had no significant effect on fatigue in patients with FM. Therefore, we sought to undertake a comprehensive systematic review of randomised controlled trials (RCTs) to evaluate the efficacy of HBOT in patients with FM. To the best of our knowledge, this will be the first systematic review conducted and reported using the highest current methodological standards to determine the effectiveness of HBOT in patients with FM. We hope this study will provide a valuable reference for future fundamental and clinical research to refine HBOT for patients with FM.
METHODS AND ANALYSIS

Study design and registration

This protocol is reported following the Preferred Reporting Items for Systematic review and Meta-Analyses Protocol (PRISMA-P) guideline. The final review will be reported following the guidelines of the PRISMA and Cochrane Handbook for Systematic Reviews of Interventions. The protocol was registered on PROSPERO, registration number CRD42022363672.

Inclusion criteria

We will include studies written in English or Chinese and eligible studies published in peer-reviewed journals. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, studies will be adopted in the final review if they meet the following inclusion criteria defined by the PICOS (patient-intervention-comparison-outcome-study) elements:

- Types of participants: This study’s population should include patients diagnosed with FM according to the American College of Rheumatology definition criteria. Trials will be eligible if they include patients with FM regardless of age, sex or any healthcare setting.
- Types of interventions: The studies will include RCTs, and the intervention will be HBOT alone or in combination with other conventional treatments. There are no restrictions on the intervention’s frequency, duration or specific pressure.
- Types of comparators: All of the following controls will be deemed eligible: placebo or sham control, conventional treatment, no intervention and no HBOT under the same treatment programme.
- Types of outcome measures: Primary outcomes will include pain (measured using the Visual Analogue Scale, Numerical Rating Scale or other validated measurements) and functional impairment (measured with the Fibromyalgia Impact Questionnaire); secondary outcomes will include quality of life (measured with the 36-item Short-Form Health Survey, quality of life or other validated measurements), sleep quality (measured with the Pittsburgh Scale, Pittsburgh Sleep Quality Index or other validated measurements), level of fatigue (measured with the Fatigue Assessment Scale, Multidimensional Fatigue Inventory or other validated measurements), level of depression and anxiety (measured with the Hospital Anxiety and Depression Scale, Hamilton Depression Scale-Depression or other validated measurements) and level of stress (measured with the Perceived Stress Scale 4 or other validated measurements).
- Types of studies: RCTs written in English or Chinese and published as full-text manuscripts will be included. Comments, letters, poster displays, conference proceedings, abstracts, dissertations, editorials, agreements, case reports and unavailable data will be excluded from the analysis.

Search strategy

The following 10 key databases will be searched from inception through December 2022 to identify relevant RCTs examining the effectiveness of HBOT in patients with FM: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO, CINAHL, Physiotherapy Evidence Database (PEDro), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, WANFANG database and the Chinese Scientific Journal Database (VIP).

The search will be performed using a combination of subject terms and free-text words. Furthermore, we will manually search the reference lists of all included trials, relevant reviews and publications to identify potentially eligible studies. Online supplemental appendix 1 presents the specific search strategies for each database.

Study selection

EndNote V.X9 software will be used to import the retrieved records and remove duplicates. Using the predefined criteria, two review authors (YH and XH) will independently screen the titles, abstracts and keywords of the remaining articles. After preliminary screening, the full texts of all the remaining studies will be carefully reviewed, and the reasons for exclusion will be documented in detail. Any disagreements will be resolved through discussion or negotiation with a third author (XL). The study screening and selection plan are shown in figure 1.

Data extraction and management

Two review authors (YH and XH) will extract the relevant data from the included studies using a predesigned data collection Excel form. The form will contain the following information:

- General information: article title, journal, year of publication, first author, country of study, aim of study, trial registration, study funding source and possible conflicts of interest.
- Study characteristics: Study design, randomisation method, blinding method, allocation concealment and completeness of outcome data.
- Participants: Age, gender, sample size, baseline participant characteristics.
- Treatment: Interventions (duration, frequency and course of HBOT) and the control group intervention description.
- Outcomes: Primary and secondary outcomes, follow-up time and adverse events.

Two review authors (YH and XH) will independently extract the above data, and any disagreements will be resolved through discussion or consultation with a third author (XL).

Quality assessment

Two authors (YH and XH) will independently assess the risk of bias of each study by using the PEDro Scale. Possible disagreements will be resolved by discussions or
consultations with a third author (XL). The PEDro Scale is considered a valid and reliable measure of the methodological quality of RCTs in physiotherapy.\textsuperscript{51} The scale comprises 11 itemised criteria. Considering that the first item is not used to calculate scores, the scale has a possible range of 0–10, with higher scores revealing higher quality. On this scale, the cut-off for high-quality methodology is a score \( \geq 6 \) points.\textsuperscript{50, 51}

**Data analysis and synthesis**

Cochrane Review Manager V.5, provided by the Cochrane Collaboration, will be used for the meta-analysis. In our study, a meta-analysis of the effects of HBOT will be conducted if at least two studies used homogeneous outcome measures or measured similar constructs.

The summary results will be computed differently depending on the data type. For continuous data, the standardised mean differences and CIs will be calculated. Heterogeneity across the studies will be assessed via the \( \chi^2 \) test and I\(^2\) statistic.\textsuperscript{47, 52} If \( p > 0.1 \) and I\(^2\) ≤ 50\%, the data combination will use a fixed-effects model. If \( p > 0.1 \) and I\(^2\) > 50\%, the data combination will use a random effects model, and substantial heterogeneity will be considered in this instance; if \( p \leq 0.1 \), the statistical significance will be considered, and a subgroup analysis or narrative description will be conducted.\textsuperscript{47}

When appropriate data are available, prespecified subgroups will be conducted based on the oxygen dose received during HBOT (pressure, time and length of treatment course), nature of the comparator treatment, degree of pain and age (adults vs children) to explore factors that might be related to the strength of the effect.

If more than 10 trials are included in the results of a meta-analysis, we will build a funnel chart to explore the potential for publication bias.

Where appropriate, sensitivity analyses will be conducted to investigate the effects of study quality and missing data on the overall meta-analysis summary estimate and examine the results' robustness and reliability.

We will evaluate the overall quality of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. Depending on the assessment, we will rate it as high, moderate, low or very low. Two authors (YH and XH) will independently use GRADEpro GDT (https://gradepro.org) to assess the quality of evidence, and possible differences will be resolved through discussion or consultation with a third author (XL).

**Patient and public involvement**

None.
ETHICS AND DISSEMINATION

Ethical approval will not be required for this review. The results of this research will be disseminated in a peer-reviewed journal.

DISCUSSION

As a potentially devastating disease, FM seriously affects the activities of daily living and causes a huge economic burden on individuals and society. Studies have indicated that 50% of patients’ symptoms do not improve significantly with pharmacotherapy. Recently, many complementary therapies have been explored, and HBOT has attracted attention as a non-invasive, non-drug approach. Ablin et al showed that HBOT can significantly improve pain, quality of life and social function in FM triggered by traumatic brain injury compared with pharmacological intervention, while increasing brain activity in the frontal and parietal regions. Moreover, this therapy is considered to play an important role in the management of chronic pain by reducing the production of glial cells and inflammatory mediators. Non-pharmacological therapy has been strongly recommended in multiple clinical guidelines for the treatment of FM. However, the inconsistent results of HBOT on patients with FM have made it difficult to conclude its safety and effectiveness. Curtis et al reported that sleep in patients with FM could be continuously improved at 3 months follow-up after HBOT. Guggino et al reported that HBOT could improve patients’ sleep quality, but the total sleep time per night is not improved. On the contrary, Atzeni et al showed that HBOT has no significant improvement in sleep quality in patients with FM. Therefore, we intend to conduct a systematic review and meta-analysis to quantify the safety and efficacy of HBOT in FM treatment, to provide reliable reference information for patients and physicians when choosing FM treatment options. The GRADE (The Grading of Recommendations Assessment, Development and Evaluation) framework was used to summarise the effect estimates to achieve a more comprehensive and objective assessment of the current evidence in this area.

There are several limitations for this study to consider. First, the number of RCTs on FM may be limited, and could lead to conclusions with relatively weak generalisability. Furthermore, because the duration and pressure of the HBOT protocols used in various studies may differ, the conclusions may be somewhat biased. Next, studies published in languages other than English or Chinese will be excluded because of language limitations, which could lead to language bias.

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Contributors Concept and design of the study: YH, XH, NS and XL; Protocol registration on the PROSPERO database: XH; Search strategy design: XY; Design of data acquisition, analysis and interpretation: YH, XH, NS, XY and XL; Drafting the protocol critically: NS, XL. All authors have read and approved the final protocol. XL is the guarantor of this protocol.

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ORCID iDs

Yuyi Han http://orcid.org/0000-0001-5041-1340

Nianyi Sun http://orcid.org/0000-0002-3524-4828

Xueyong Liu http://orcid.org/0000-0001-6087-5851

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