INPLASY PROTOCOL

To cite: Kulshreshtha et al. Assessment of the efficacy and safety of the hyperbaric oxygen therapy on pain in patients with fibromyalgia: A systematic review and meta-analysis protocol. Inplasy protocol 2022100001. doi: 10.37766/inplasy2022.10.0001

Received: 01 October 2022

Published: 01 October 2022

Corresponding author:
Poorvi Kulshreshtha

poorvi77@gmail.com

Author Affiliation:
All India Institute of Medical Sciences.

Support: **Not applicable.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Assessment of the efficacy and safety of the hyperbaric oxygen therapy on pain in patients with fibromyalgia: A systematic review and meta-analysis protocol

Kulshreshtha, P[1]; Neyaz, O[2]; Begum, S[3]; Yadav, RK[4]; Deepak, KK[5].

Review question / Objective: **A few studies have addressed the efficacy of hyperbaric oxygen therapy in patients with fibromyalgia. However, these studies have been inconclusive so far. There is no graded evidence in the form of a systematic review or meta-analysis concerning the administration of hyperbaric oxygen therapy to patients with fibromyalgia. The proposed study would be carried out to assess the efficacy and safety of hyperbaric oxygen therapy in reducing pain in patients with fibromyalgia. Primary Objective: To compare the efficacy of HBOT with the standard conventional therapy in patients with fibromyalgia of age 18 years and more. Secondary Objectives: i. To compare the adverse effects (for safety) of HBOT with the standard conventional therapy in patients with fibromyalgia of age 18 years and more; ii. To compare the change in the quality of life, sleep quality, functional impairment, depression, anxiety, and psychological distress by HBOT as compared with the standard conventional therapy in patients with fibromyalgia of age 18 years and more.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 October 2022 and was last updated on 01 October 2022 (registration number INPLASY2022100001).

INTRODUCTION

Review question / Objective: **A few studies have addressed the efficacy of hyperbaric oxygen therapy in patients with fibromyalgia. However, these studies have been inconclusive so far. There is no graded evidence in the form of a systematic review or meta-analysis concerning the administration of hyperbaric oxygen therapy to patients with fibromyalgia. The proposed study would be carried out to assess the efficacy and safety of hyperbaric oxygen therapy in reducing pain in patients with fibromyalgia. Primary Objective: To compare the efficacy**

of HBOT with the standard conventional therapy in patients with fibromyalgia of age 18 years and more. Secondary Objectives: i. To compare the adverse effects (for safety) of HBOT with the standard conventional therapy in patients with fibromyalgia of age 18 years and more; ii. To compare the change in the quality of life, sleep quality, functional impairment, depression, anxiety, and psychological distress by HBOT as compared with the standard conventional therapy in patients with fibromyalgia of age 18 years and more.

Rationale: Hyperbaric oxygen therapy (HBOT) is a promising medical technology in which people breathe 100% oxygen under high atmospheric pressure. Of late, HBOT is being utilized as a treatment modality for fibromyalgia, where its beneficial effect has been attributed to the stimulation of nitric oxide synthesis. Increased nitric oxide alleviates hyperalgesia and releases endogenous opioids responsible for the anti-nociceptive effects of HBOT. The HBOT improves plasma and tissue oxygen content, due to which blood vessels proliferate, which promotes tissue recovery, thus decreasing tissue hypoxia that causes pain. HBOT may also alter the brain pain-processing activity, especially by changing the hemodynamics. However, there are no previously published systematic reviews and meta-analyses on assessing the efficacy and safety of HBOT for fibromyalgia, and evidence of its efficacy and safety is inconclusive. Therefore, the proposed study intends to adopt the systematic evaluation and meta-analysis to assess the clinical efficacy and safety of HBOT for fibromyalgia and offer scientific evidence of HBOT for Fibromyalgia.

Condition being studied: Fibromyalgia (FM) is a debilitating psychosomatic illness with widespread chronic pain as its hallmark. This condition is more frequent in women than in men (9:1, respectively) and occurs in up to 2-4% of the population within Western societies. Fibromyalgia affects the quality of life and imposes an economic burden due to loss of productivity caused by absenteeism and disability. It is also characterized by diffuse musculoskeletal pain, fatigue, sleep disturbance, stiffness, mood changes, etc. One can only speculate whether these associated symptoms are the causes or effects of this chronic pain syndrome. The heterogeneity of symptoms and ineffective treatment raise questions about the current diagnostic criteria. The phenomenon of central sensitization [attributed to a higher gain setting of pain processing] and peripheral tissue abnormalities in fibromyalgia have been discussed in the literature. The uncertain diagnosis of FM disorder places it in a virtual pain continuum ranging from predominantly peripheral nociceptive, to predominantly neuropathic, to largely centralized pain conditions. Current treatments for fibromyalgia include medication and self-care strategies that emphasize reducing pain, improving sleep, and alleviating other co-existing symptoms. The FDA has approved only three drugs, including pregabalin, duloxetine, and milnacipran, for use in fibromyalgia. Considerable evidence for therapeutic efficacy is present in the literature with respect to tricyclic antidepressants (amitriptyline) for use in patients with fibromyalgia.

METHODS

Search strategy: The search strategy is designed and would be performed by two authors (PK and ON) under the supervision of a senior investigator (KKD). No date restriction would be applied to the literature search. We will systematically search medical subject headings and keywords associated with HBOT in treating fibromyalgia based on the following databases: MEDLINE/ PubMed, Web of Science, PEDro, Cochrane Library Central Register of Controlled Trials, Embase and Scopus. Meanwhile, we will also search the relevant literature in Google Scholar to identify possible nonindexed published studies. The keywords for searching the databases for relevant literature are as follows:

#1. "Fibromyalgia" [MeSH] OR "Fibromyalgia" [Title/Abstract] OR "FM"

[Title/Abstract] OR "FMS" [Title/Abstract] OR "Fibrositis" [Title/Abstract]
#2. "Hyperbaric Oxygenation" [MeSH Terms] OR "Hyperbaric Oxygenation" [Title/Abstract] OR "Hyperbaric Oxygenations" [Title/Abstract] OR "Oxygenations, Hyperbaric" [Title/Abstract] OR "Hyperbaric Oxygen Therapy" [Title/Abstract] OR "Hyperbaric Oxygen Therapies" [Title/Abstract] OR "Oxygen Therapies, Hyperbaric" [Title/Abstract] OR "Oxygen Therapy, Hyperbaric" [Title/Abstract] OR "Therapies, Hyperbaric Oxygen" [Title/Abstract] OR "Therapy, Hyperbaric Oxygen" [Title/Abstract] OR "Oxygenation, Hyperbaric" [Title/Abstract]
#3. #1 AND #2
The reference lists of identified original articles or reviews would also be searched manually for relevant articles. The http://www.clinicaltrial.gov would be searched for potential studies being conducted or planned.

Participant or population: Patients with a diagnosis of fibromyalgia of age 18 years and more.

Intervention: HBOT (Hyperbaric oxygen therapy).

Comparator: Patients with fibromyalgia who are on conventional treatment.

Study designs to be included: Only the Randomized controlled trials (RCTs) that investigated the efficacy and safety of HBOT for FM will be selected for inclusion. All RCTs comparing HBOT with conventional treatment in patients with fibromyalgia at least in one arm, open-label, single or double-blind studies irrespective of country of origin or ethnicity or duration of treatment would be included.

Eligibility criteria: For this study, only articles written in the English language would be considered eligible. To be included in the final review, studies had to be published as full-text original articles in international, peer-reviewed journals. Non-randomized controlled trials, literature reviews, case reports, studies with animal models of pain, specialist experience, letters to editors, commentaries, editorials, research articles without available full texts, book chapters, conference papers, theses, abstract-only articles, and repeated documents will not be collected.

Information sources: All electronic databases would be the source of information for the present systematic review, including MEDLINE/ PubMed, Web of Science, PEDro, Cochrane Library Central Register of Controlled Trials, Embase and Scopus. Meanwhile, we will also search the relevant literature in Google Scholar to identify possible nonindexed published studies.

Main outcome(s): The primary outcome would be the clinical effect on pain. All outcome parameters would be assessed by comparing the final values (obtained) after completion of HBOTtherapy) with the baseline ones irrespective of the duration of treatment.

Additional outcome(s): The secondary outcomes will contain the following items: adverse effects of HBOT; quality of life; functional impairment using the Fibromyalgia Impact questionnaire; Questionnaire-based test to assess depression, anxiety, and psychological distress; Sleep quality scale. All secondary outcome parameters would also be assessed by comparing the final values (obtained) after completion of HBOTtherapy) with the baseline ones irrespective of the duration of treatment.

Data management: After removing duplicate records, two reviewers (PK and ON) would independently screen titles and abstracts for the first-step evaluation. Following the screening phase, the other two reviewers (SB, RKY) would independently evaluate the remaining articles' full text to determine eligibility for inclusion in the final review. Disagreements among the reviewers would be resolved by discussion with senior investigator (KKD) until reaching a final consensus.

Quality assessment / Risk of bias analysis: To assess the risk of bias in included

studies, we used the Cochrane RoB 2 tool. Two review authors will independently assess the risk of bias in included studies according to the criteria in the Cochrane Handbook for Systematic Reviews of Interventions as follows: the random sequence generation, allocation concealment, incomplete outcome data, blinding (participants, personnel, and outcome assessment), selective reporting, and other biases. After that, another two review authors will independently judge each study as having a high or unclear risk of bias. In addition, we will resolve any inconsistencies by contacting the corresponding author in obtained literature, consulting a third party, or conducting internal discussions.

Strategy of data synthesis: Review Manager (Revman, Version 5.4) software provided by the Cochrane Collaboration will be used for data analysis. Determination of HBOT efficacy: For continuous variables, standardized mean difference (SMD) and 95% confidence interval (CI) will be used for statistics. For dichotomous data, we are to apply relative risk with 95% confidence intervals for analysis. Handling missing data. Where data are missing, we will attempt to communicate with the first author or correspondent author by e-mail or phone to acquire the complete data. If the contact fails, we will start our analysis according to the existing data. The probable effect of incomplete data will also be included in the discussion. Determination of heterogeneity: The heterogeneity tests of each outcome will be performed using the Chi-squared test and I2 statistic. There is substantial heterogeneity among the trials when I2 ≥ 50%, but low or no heterogeneity when I2< 50%. Moreover, we will conduct subgroup analysis or sensitivity analysis to check the possible reasons when heterogeneity is substantial. Analysis of reporting bias Funnel plots will be planned to visually investigate the asymmetry and potential publication bias along with the quantitatively Egger test. Data synthesis Related analyses will be performed in RevMan 5.3 software (The Cochrane Collaboration, Oxford, England). If heterogeneity is minor (I2 < 50%), we will apply the fixed-effect approach for meta-analysis. However, if heterogeneity is substantial (I2 ≥ 50%), we will use the random-effect approach for meta-analysis. On the other hand, we will carry out the narrative analysis if there is significant heterogeneity or an inability to judge the source of it. Determination of evidence quality. We will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group approach to determine the evidence quality for all outcomes. The quality of evidence quality will be classified as high, moderate, low, or very low. Review Manager (Revman, Version 5.4) software provided by the Cochrane Collaboration will be used for data analysis.

Subgroup analysis: If available, subgroup analyses will be performed following items in our plan: variables for hyperbaric oxygenation (high/low atmospheric pressure, duration of single session), male/female, and total duration of treatment.

Sensitivity analysis: The sensitivity analysis will be employed to investigate each study's influence on the main outcomes using remove one at a time. Meta-regression will also be planned.

Language restriction: Language will be limited to English.

Country(ies) involved: India.

Other relevant information: None.

Keywords: Hyperbaric oxygen therapy; Fibromyalgia; systematic review; Meta-analysis.

Dissemination plans: The systematic review and meta-analysis would be published in a peer-reviewed journal and presented at conferences.

Contributions of each author:
Author 1 - Poorvi Kulshreshtha - Study conceptualization, Literature searching, quality assessment, data synthesis, and manuscript writing.

Email: poorvi77@gmail.com
Author 2 - Osama Neyaz - Literature searching and quality assessment.
Email: osamaneyaz@gmail.com
Author 3 - Shahina Begum - Data extraction, data synthesis.
Email: shahina_appe@yahoo.com
Author 4 - Raj Kumar Yadav - Data extraction and data synthesis.
Email: raj.pmr@aiimsrishikesh.edu.in
Author 5 - Kishore Kumar Deepak - Quality assessment, proofreading & correction of the final manuscript, final approval for submission.
Email: kkdeepak@gmail.com