## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia: A Systematic Review and Meta-analysis |
| **AUTHORS** | Chen, Xinxin; You, Jiuhong; Ma, Hui; Zhou, Mei; Huang, Cheng |

## VERSION 1 – REVIEW

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| **REVIEWER** | vaishali k<br>Manipal College of Health Professions, Physiotherapy |
| **REVIEW RETURNED** | 18-Apr-2022 |

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| **GENERAL COMMENTS** | We congratulate the authors for performing the systematic review and meta-analysis. I have a few comments to address:<br>Need of the study requires to be strengthened further<br>Eligibility criteria- needs elaboration of exclusion criteria<br>Statistical analysis results for the present SR is not mentioned |

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| **REVIEWER** | Robin Christensen<br>Frederiksberg and Bispebjerg Hospital, Parker Institute |
| **REVIEW RETURNED** | 25-Apr-2022 |

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| **GENERAL COMMENTS** | The authors vaguely argue that their objective is "to qualify the safety and overall efficacy of HBOT for FM."; Please phrase it as a more "standard objective"<br><br>Also I would strongly recommend that the authors focus on all the RCT's available (not cohorts!); it is very confusing to read the attempt(s) to lump RCT data with Cohort data(?)<br><br>Q1: It was unclear to me whether the protocol had been pre-specified, and also pre-registered (e.g.on PROSPERO). Please update directly in the body of the manuscript.<br><br>Q2: In terms of outcomes, the authors should attempt to perform meta-analysis (quantitative synthesis) on all the "Core Outcomes" for Fibromyalgia (i.e. based on 3 eligible RCTs?)<br><br>Q3: Please attempt to provide quantitative evidence synthesis on the entire Core Outcome Set:<br>*pain,<br>*tenderness,<br>*fatigue,<br>*patient global,<br>*multidimensional function and<br>*sleep disturbance domains<br>- which should be measured and available from all FM clinical trials (see Mease et al, J Rheum 2009) |

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| | + Harms: SAE's, Withdrawals due to AEs, Total Withdrawals, and Number of Deaths<br><br>Q4: Meta-Analysis: Please decide - a priori - to use Random Effects Model (per default) rather than letting the I-squared guide you (most organisations would expect "heterogeneity" as the base case); see Riley et al, BMJ 2011<br><br>Q5: After a succesful evidence synthesis the authors should attempt to communicate (and interpret) using the GRADE format<br><br>Thanks! |

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| **REVIEWER** | Basem Al-Omari<br>Khalifa University of Science and Technology, College of Medicine and Health Sciences |
| **REVIEW RETURNED** | 29-Apr-2022 |

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| **GENERAL COMMENTS** | Abstract:<br>Precise and straight to the point.<br>Introduction:<br>Well written introduction<br>Methods:<br>Appropriate search strategy, screening, quality assessment, and data extraction. Good justification of the statistical analysis method.<br>Has a protocol for this SR been registered?<br>Table 1: Should be provided as supplementary material and it should show the actual search with the number of hits per search then combined.<br>Inconsistency in the language fluctuating between past and future tense in the methods section. It should be all in past tense. Please consider revising.<br>Line 109: “All interventions except HBOT should be consistent between the two groups”. Do you mean all variables related to participants or interventions used to treat FM other than HBOT? Interventions cannot be consistent between the experimental and control group unless you are referring to treatment for other conditions that could have an impact on the outcome of interest. However, participants’ variable should be consistent. I think this need to be clarified.<br><br>Results:<br>I suggest adding a section to discuss the treatment and control. The reader cannot identify what did the included studies compared HBOT with. This information can also be added to table 2.<br>Table 2: Since none of the studies showed a clear follow up, I would suggest removing this column from the table and just mention this in the text. “Number of sessions” in column 7 in the table; I suggest adding the length of treatment and discuss if this had an impact on the outcome.<br>Line 187: I suggest presenting more details about the risk of bias for the 3 RCTs. The figure shows clearly that Izquierdo 2020 has lower risk of bias than the other 2 studies.<br>This SR is presenting very limited results. No explanation of the HBOT procedure. Adverse events are mentioned briefly in Line 216-224. There should be more details about this and a table presenting procedure, primary and secondary outcome, adverse events, and complications.<br><br>Discussion: |

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| | Paragraph 1 (Line 228-235) is repeated background information. I suggest removing it.<br>Saying that “HBOT for FM could be considered safe” in the first paragraph is completely inappropriate. This SR is to investigate the effectiveness of HBOT. Furthermore, in the results the authors mentioned that only 2 studies investigated the adverse events.<br>The discussion is not well written and it is difficult to read. For example: “Even with randomization and blinding in analysis, there was no blinding performed on the participants due to the inherent difficulty conducting sham control in HBOT trials”. How did the authors analgised randomisation and blinding? These cannot be analysed. Furthermore, the authors jump between ideas abruptly without fully explain and discuss their outcome.<br>Conclusion:<br>There is no conclusion section for the study. This sentence in line 286 as a conclusion “the present study shows that HBOT has a significant effect on FM” is inaccurate. The SR outcome of interest in relieving pain for FM. This is a very broad conclusion without supporting evidence. |

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| **REVIEWER** | Annalisa De Silvestri<br>Foundation IRCCS Polyclinic San Matteo |
| **REVIEW RETURNED** | 19-Sep-2022 |

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| **GENERAL COMMENTS** | Please introduce a paragraph stating aims and outcomes of the meta_analyses.<br><br>Please explain how 18 papers were eliminated between removal of duplicates (N=84) and beginning of screening of title/abstract(N=66) |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1: We congratulate the authors for performing the systematic review and meta-analysis. I have a few comments to address:
Reviewer point #1: Need of the study requires to be strengthened further
Author response #1: Thank you for the suggestion. We have added some content to strengthen the requires of the study on page 3, lines 99-108 of Manuscript (clean copy).

Reviewer point #2: Eligibility criteria- needs elaboration of exclusion criteria
Author response #2: Thank you for the suggestion. We have added the elaboration of exclusion criteria: animal studies, reviews, duplicate publications, irrelevant studies, editorial materials, patients, case reports or meeting abstracts.

Reviewer point #3: Statistical analysis results for the present SR is not mentioned
Author response #2: Thank you for the suggestion. We have added SR in the result section on page 11-12, lines 276-353 of Manuscript (clean copy) and discussed the outcomes of SR in the discussion section on page 14, lines 368-397 of Manuscript (clean copy).

Reviewer 2:
Reviewer point #1: The authors vaguely argue that their objective is "to qualify the safety and overall efficacy of HBOT for FM."; Please phrase it as a more "standard objective"
Author response #1: Thank you for the suggestion. We have improved the objective of our study on page 3, lines 102-108 of Manuscript (clean copy).

Reviewer point #2: Also I would strongly recommend that the authors focus on all the RCT's available (not cohorts!); it is very confusing to read the attempt(s) to lump RCT data with Cohort data(?)

Author response #2: Thank you for the suggestion. We have conducted a meta-analysis of the same research type (only three RCTs) on the pain relief outcome (Figure 3).

Reviewer point #3: It was unclear to me whether the protocol had been pre-specified, and also pre-registered (e.g.on PROSPERO). Please update directly in the body of the manuscript.
Author response #3: Thank you for the suggestion. We registered this SR on October 1, 2021. PROSPERO registration number is CRD42021282920. We have added the registration information in the main text of the manuscript on page 4, lines 112-113 of Manuscript (clean copy).

Reviewer point #4: In terms of outcomes, the authors should attempt to perform meta-analysis (quantitative synthesis) on all the "Core Outcomes" for Fibromyalgia (i.e. based on 3 eligible RCTs?)
Author response #4: Thank you for the suggestion. Pain relief was the primary outcome measure and could be meta-analysed (from three RCTs) (Figure 3). Other Core Outcomes for Fibromyalgia were analysed descriptively because of the limited number of studies or limited available data that could be combined.

Reviewer point #5: Please attempt to provide quantitative evidence synthesis on the entire Core Outcome Set:
*pain,
*tenderness,
*fatigue,
*patient global,
*multidimensional function and
*sleep disturbance domains
- which should be measured and available from all FM clinical trials (see Mease et al, J Rheum 2009)
+ Harms: SAE's, Withdrawals due to AEs, Total Withdrawals, and Number of Deaths
Author response #5: Thank you for the suggestion. We only performed meta-analysis for the primary outcome (pain relief). Other indicators (tenderness, fatigue, multidimensional function, patient global, sleep disturbance, and adverse events) were analyzed descriptively because of the limited number of studies or limited available data that could be combined. As the reviewers proposed that very limited results of SR were presented, we included some studies which excluded before because of not eligible for meta-analysis to add the part of systematic review. Therefore, we have added SR in the result section on page 11-12, lines 276-353 of Manuscript (clean copy) and discussed the outcomes of SR in the discussion section on page 14, lines 368-397 of Manuscript (clean copy). We have rewritten the Abstract.

Reviewer point #6: Meta-Analysis: Please decide - a priori - to use Random Effects Model (per default) rather than letting the I-squared guide you (most organisations would expect "heterogeneity" as the base case); see Riley et al, BMJ 2011
Author response #6: Thank you for the suggestion. We have improved our approach better on page 6, lines 199-205 of Manuscript (clean copy): Forest plot tests were conducted, and meta-regression analysis was used to test heterogeneity. The chi-square 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 (1).
Reference:
(1) Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011 Feb 10;342:d549. doi: 10.1136/bmj.d549. PMID: 21310794.

Reviewer point #7: After a successful evidence synthesis the authors should attempt to communicate (and interpret) using the GRADE format

Author response #7: Thank you for the suggestion. We have used GRADE system to grade the quality of 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 larger effect. The GRADE evidence profile is shown in Table 3. We have added the discussion about GRADE analysis of pain relief on page 15-16, lines 452-459 of Manuscript (clean copy).

Reviewer 3:
Abstract:
Precise and straight to the point.
Introduction:
Well written introduction
Methods:
Reviewer point #1: Appropriate search strategy, screening, quality assessment, and data extraction. Good justification of the statistical analysis method. Has a protocol for this SR been registered?
Author response #1: We registered this SR on October 1, 2021. PROSPERO registration number is CRD42021282920. And we have added the registration information in the main text of the manuscript on page 4, lines 112-113 of Manuscript (clean copy).

Reviewer point #2: Table 1: Should be provided as supplementary material and it should show the actual search with the number of hits per search then combined.
Author response #2: Thank you for the suggestion. We have uploaded Supplementary appendix A. The search strategy is shown in Supplementary appendix A.

Reviewer point #3: Inconsistency in the language fluctuating between past and future tense in the methods section. It should be all in past tense. Please consider revising.
Author response #3: Thank you for the suggestion. We have unified the methodological content in past tense.

Reviewer point #4: Line 109: “All interventions except HBOT should be consistent between the two groups”. Do you mean all variables related to participants or interventions used to treat FM other than HBOT? Interventions cannot be consistent between the experimental and control group unless you are referring to treatment for other conditions that could have an impact on the outcome of interest. However, participants’ variable should be consistent. I think this need to be clarified.
Author response #4: I apologize for this inappropriate expression. We have deleted the sentence.

Results:
Reviewer point #5: I suggest adding a section to discuss the treatment and control. The reader cannot identify what did the included studies compared HBOT with. This information can also be added to table 2.
Author response #5: Thank you for the suggestion. We have added a section to discuss the treatment and control on page 14-15, lines 398-428 of Manuscript (clean copy). And we have added the information of control group to Table 1.

Reviewer point #6: Table 2: Since none of the studies showed a clear follow up, I would suggest removing this column from the table and just mention this in the text. “Number of sessions” in column 7 in the table; I suggest adding the length of treatment and discuss if this had an impact on the outcome.
Author response #6: Thank you for the suggestion. We have removed “follow-up” column from the Table 1 and just mentioned this in the discussion. We have added the length of treatment in Table 1

and discuss if this had an impact on the outcome on page 14-15, lines 405-428 of Manuscript (clean copy).

Reviewer point #7: Line 187: I suggest presenting more details about the risk of bias for the 3 RCTs. The figure shows clearly that Izquierdo 2020 has lower risk of bias than the other 2 studies.
Author response #7: Thank you for the suggestion. We have presented more details about the risk of bias for the three RCTs on page 9, lines 230-236 of Manuscript (clean copy).

Reviewer point #8: This SR is presenting very limited results. No explanation of the HBOT procedure. Adverse events are mentioned briefly in Line 216-224. There should be more details about this and a table presenting procedure, primary and secondary outcome, adverse events, and complications.
Author response #8: Thank you for the suggestion. We included some studies which excluded before because of not eligible for meta-analysis to add the part of systematic review. Therefore, we have added SR in the result section on page 11-12, lines 276-353 of Manuscript (clean copy) and discussed the outcomes of SR in the discussion section on page 14, lines 368-397 of Manuscript (clean copy). We have added a section to discuss the HBOT procedure on page 14-15, lines 405-428 of Manuscript (clean copy). We rewritten the results of adverse events on page 12, lines 345-353 of Manuscript (clean copy) and added the discussion about adverse events on page 14, lines 379-397 of Manuscript (clean copy). We have added adverse events in Table 1.

Discussion:
Reviewer point #9: Paragraph 1 (Line 228-235) is repeated background information. I suggest removing it.
Author response #9: Thank you for the suggestion. We have removed this repeated background information

Reviewer point #10: Saying that “HBOT for FM could be considered safe” in the first paragraph is completely inappropriate. This SR is to investigate the effectiveness of HBOT. Furthermore, in the results the authors mentioned that only 2 studies investigated the adverse events.
Author response #10: Thank you for the suggestion. We have removed this inappropriate sentence. Actually, our study aims to investigate the efficacy and safety of hyperbaric oxygen therapy (HBOT) for fibromyalgia (FM). As the reviewers proposed that very limited results of SR were presented, we included some studies which excluded before because of not eligible for meta-analysis to add the part of systematic review. Therefore, we rewritten the results of adverse events on page 12, lines 345-353 of Manuscript (clean copy) and added the discussion about adverse events on page 14, lines 379-397 of Manuscript (clean copy). We have added adverse events in Table 1.

Reviewer point #11: The discussion is not well rewritten and it is difficult to read. For example: “Even with randomization and blinding in analysis, there was no blinding performed on the participants due to the inherent difficulty conducting sham control in HBOT trials”. How did the authors analyze randomization and blinding? These cannot be analysed. Furthermore, the authors jump between ideas abruptly without fully explain and discuss their outcome.
Author response #11: Thank you for the suggestion. We have rewritten the discussion and improved the readability of this section on 14-16, lines 368-471 of Manuscript (clean copy). And we have removed this inappropriate sentence.

Conclusion:
Reviewer point #12: There is no conclusion section for the study. This sentence in line 286 as a conclusion “the present study shows that HBOT has a significant effect on FM” is inaccurate. The SR outcome of interest in relieving pain for FM. This is a very broad conclusion without supporting evidence.

Author response #12: Thank you for the suggestion. We have added the conclusion section for the study on page 14, lines 368-397 of Manuscript (clean copy). We have removed this inappropriate sentence. We have added the SR outcomes such as tenderness, fatigue, multidimensional function, patient global, sleep disturbance on page 11-12, lines 276-353 of Manuscript (clean copy). We have added some evidence in the discussion section.

Reviewer 4
Reviewer point #1: Please introduce a paragraph stating aims and outcomes of the meta_analyses.
Author response #1: Thank you for the suggestion. We have improved the objective of our study on page 3, lines 102-108 of Manuscript (clean copy). We have introduced a paragraph stating aims and outcomes of the meta-analyses on page 14, lines 368-397 of Manuscript (clean copy).

Reviewer point #2: Please explain how 18 papers were eliminated between removal of duplicates (N=84) and beginning of screening of title/abstract(N=66)
Author response #2: Thank you for the suggestion. Due to the long review period, we have re-searched the databases according to the retrieval strategy and updated the flow chart (Figure 1).