PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exercise-induced hypoalgesia after aerobic versus neck-specific exercise in acute/subacute whiplash associated disorders: Protocol for a randomised controlled trial
AUTHORS	Anarte-Lazo, Ernesto; Bernal-Utrera, Carlos; Lopez-Amor, Mario; Porras-Valencia, Eugenia; Ruy-Diaz-Rojas, Francisco Javier; Falla, Deborah; Rodriguez-Blanco, Cleofas

VERSION 1 – REVIEW

REVIEWER	Ritchie, Carrie The University of Queensland
REVIEW RETURNED	05-Apr-2022

GENERAL COMMENTS	The proposed study to investigate EIH in people with an acute/subacute whiplash injury is interesting and will add important information to existing literature. There are a few questions about the methodology that should be considered by the researchers before embarking on the project. 1. Inclusion/exclusion criteria: will individuals with a grade II whiplash injury be included regardless of current neck pain or disability? If so, as you have indicated in the introduction, approximately 60% will recover naturally. How will inclusion of fully recovered individuals affect the sample size calculation? In addition, will there be an inclusion criteria to ensure that participants will be able to participate in exercise safely? 2. Blinding: it is not clear how the RCT can be double-blind. How will the evaluator be blinded to the exercise performed by the participant? What is included within the patient information sheet/consent that enables the patient to be blinded to the type of exercise? Furthermore, there is some evidence that EIH may dissipate quickly post-exercise so the timing of PPT measurements following the exercise sessions needs to be specified (and standardized) to understand how the evaluator will be blind to the participant's group. 3. Standardized evaluation: will the order of the anatomical site for PPT testing and VAS measurement be standardized, why or why not? If so, how? 4. Measurements: a. how and when will heart rate be measured and recorded? B. Why are only two PPT measures to be taken at each site rather than three? Is there a standardized process that will occur if the two measures are markedly different? 5. Outcome: is EIH defined as an absolute or relative measure? 6. Statistical analysis: the statistical analyses to address a couple of the statements in the introduction and discussion do not appear to have been included. Firstly, how is the 'time' factor considered (e.g. how will you determine whether or not EIH is sustained at 24 hours post-exercise?)? Secondly, you may wish to consider

	regression analyses to 'establish whether the extent of EIH following exercise is determined by other factors'. 7. Strengths and limitations of this study – The authors have referenced several studies that have also examined EIH in people with whiplash using randomized protocols. Hence, this is not the first RCT evaluating EIH in people with whiplash.

REVIEWER	Palsson, Thorvaldur Aalborg University, Department of Health Science and Technology
REVIEW RETURNED	11-Apr-2022

GENERAL COMMENTS	Very well defined study on an important topic. I look forwards to seeing the results I have no comments or concerns regarding this protocol

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Carrie Ritchie, The University of Queensland

Comments to the Author:
The proposed study to investigate EIH in people with an acute/subacute whiplash injury is interesting and will add important information to existing literature. There are a few questions about the methodology that should be considered by the researchers before embarking on the project.

Dear reviewer. Thank you for your comments which have improved the quality of our manuscript.

1. Inclusion/exclusion criteria: will individuals with a grade II whiplash injury be included regardless of current neck pain or disability? If so, as you have indicated in the introduction, approximately 60% will recover naturally. How will inclusion of fully recovered individuals affect the sample size calculation? In addition, will there be an inclusion criteria to ensure that participants will be able to participate in exercise safely?
Answer: Thank you for your comment. Yes, if diagnosed with grade II WAD, subjects will be included regardless of their current neck pain intensity or disability. Given that the current study will examine immediate effects of exercise, we don't expect that natural recovery will be an issue for this particular study design Thus, we don't expect that natural recovery will significantly influence our sample size calculation and will ensure that we recruit people when pain is present.. We have clarified this point on P.6.L.149: […]and not yet recovered from neck pain when the assessment is performed.
In relation to safety of interventions, the exercises proposed have already been tested and are commonly used in the management of acute /subacute neck pain and we therefore do not expect any adverse effects.

2. Blinding: it is not clear how the RCT can be double-blind. How will the evaluator be blinded to the exercise performed by the participant? What is included within the patient information sheet/consent that enables the patient to be blinded to the type of exercise? Furthermore, there is some evidence that EIH may dissipate quickly post-exercise so the timing of PPT measurements following the exercise sessions needs to be specified (and standardized) to understand how the evaluator will be blind to the participant's group.
Answer: Thank you for rising this point. The evaluator will assess the patient, then leave the room as the patient performs the intervention with facilitation from a different investigator. When finished, the

evaluator will enter the room to re-evaluate the patient. Blinding will be maintained after the 24 hours post-intervention assessment.
Regarding the patient's blinding, as stated in methods section, they will not know of the other interventions as the information sheet refers to different interventions without specifying the details.

Finally, the timing of PPT after exercise has been included on P.7. L.169.: […] two minutes after the intervention is finished.

3. Standardized evaluation: will the order of the anatomical site for PPT testing and VAS measurement be standardized, why or why not? If so, how?
Answer: Thank you for raising this point. We have included this information on P.10. L.254: To standardize the assessment, the order will be as follows: C2, C5, tibialis anterior, and three upper limb sites. For VAS, this information can be found on P.11 L.273; Pain intensity will be evaluated always just before PPT assessment.

4. Measurements: a. how and when will heart rate be measured and recorded? B. Why are only two PPT measures to be taken at each site rather than three? Is there a standardized process that will occur if the two measures are markedly different?
Answer: Thank you for these points.
a. Heart rate will be calculated during the aerobic intervention to monitor the intervention. This is explained on P.8.L.204: Heart rate will be recorded each minute during the increase in power output and then once every 3 minutes until the end of the exercise session
b. Our aim here was to avoid any burden from extended testing of participants. Therefore, since PPT has already been considered and accepted as a reliable tool to assess pain hypersensitivity, and as previously performed in other studies, we will perform only two measures and calculate the mean. In addition, we have clarified that the evaluator will receive training to standardize their evaluation - P.6 L.137.: Before starting the study, the evaluator will be trained in the different assessments to standardize the evaluation. (Ickmans K, Malfliet A, De Kooning M, Goudman L, Hubloue I, Schmitz T, Goubert D, Aguilar-Ferrandiz ME. Lack of Gender and Age Differences in Pain Measurements Following Exercise in People with Chronic Whiplash-Associated Disorders. Pain Physician. 2017 Sep;20(6):E829-E840. PMID: 28934789; Nie H, Graven-Nielsen T, Arendt-Nielsen L. Spatial and temporal summation of pain evoked by mechanical pressure stimulation. Eur J Pain. 2009 Jul;13(6):592-9. doi: 10.1016/j.ejpain.2008.07.013. Epub 2008 Oct 15. PMID: 18926745; Florencio LL, Giantomassi MC, Carvalho GF, Gonçalves MC, Dach F, Fernández-de-Las-Peñas C, Bevilaqua-Grossi D. Generalized Pressure Pain Hypersensitivity in the Cervical Muscles in Women with Migraine. Pain Med. 2015 Aug;16(8):1629-34. doi: 10.1111/pme.12767. Epub 2015 Apr 30. PMID: 25929269) w

5. Outcome: is EIH defined as an absolute or relative measure?
Answer: We will define EIH but the percentage change as it has been described previously. Changes can be found on P.11.L.264: Relative EIH will be defined as a significant positive change in PPTs, that is, when PPT increases after exercise, according to the following formula: [(PPTPostExercise – PPTPreExercise)/PPTPreExercise)] x 100.

6. Statistical analysis: the statistical analyses to address a couple of the statements in the introduction and discussion do not appear to have been included. Firstly, how is the 'time' factor considered (e.g. how will you determine whether or not EIH is sustained at 24 hours post-exercise?)? Secondly, you

may wish to consider regression analyses to ‘establish whether the extent of EIH following exercise is determined by other factors’.
Answer: Thank you for these points. This section has been modified. We have considered a regression analysis to establish correlations between variables. Information can be found on P.13.L.317: Associations between the extent of EIH and other variables will be analyzed via regression analysis. Regarding time, we have clarified that intragroup and between group analysis will be performed both in the short term and 24 hours after the intervention, as now described on P.12.L.308

7. Strengths and limitations of this study – The authors have referenced several studies that have also examined EIH in people with whiplash using randomized protocols. Hence, this is not the first RCT evaluating EIH in people with whiplash.
Answer: We agree and this section has been modified.

Reviewer: 2
Dr. Thorvaldur Palsson, Aalborg University

Comments to the Author:
Very well defined study on an important topic. I look forwards to seeing the results. I have no comments or concerns regarding this protocol.

Dear reviewer
Thank you for your comments.

Reviewer: 1
Competing interests of Reviewer: I declare no competing interests, and consent to the publication of this review.

Reviewer: 2
Competing interests of Reviewer: None

VERSION 2 – REVIEW

REVIEWER	Ritchie, Carrie The University of Queensland
REVIEW RETURNED	09-Jul-2022

GENERAL COMMENTS	The authors have addressed all of my comments. Best wishes with the study.