

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A Cross-over Randomized Controlled Trial of the Effect of Cervical Manipulation on Vertebral Artery and Cerebral Hemodynamics in Patients with Chronic Neck Pain
<b>AUTHORS</b>	Moser, Nicholas; Mior, Silvano; Noseworthy, Michael; Côté, Pierre; Wells, Greg; Behr, Michael; Triano, John

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Roger Engel Macquarie University Australia
<b>REVIEW RETURNED</b>	18-Aug-2018

<b>GENERAL COMMENTS</b>	<p>Comments</p> <p>The manuscript describes the results from a crossover randomized controlled trial designed to determine whether cervical manipulation produces clinically meaningful changes in vertebral and cerebral hemodynamics compared to a neutral neck position or neck rotation in adult patients with chronic neck pain. The trial is well-designed and appropriately conducted. The authors do not overstate the meaning of their results and adequately highlight the key limitations in the study. The manuscript will add to the body of literature on the safety associated with cervical manipulation and the possible mechanism/s underpinning vertebrobasilar artery stroke.</p> <p>I recommend the manuscript be accepted for publication subject to some minor comments listed below:</p> <ol style="list-style-type: none"><li>1. Page 8, lines 6-12: The 4 sentences included in this section appear to be repeated in the following paragraph (Page 8, lines 14-20).</li><li>2. Page 8, lines 9-12: In discussing the changes in BOLD signals, the authors offer the following explanation: "However, when examining the aforementioned areas specifically for changes in blood flow using ASL, no significant changes were observed between any of the test head conditions. This strongly suggests that the observed increased functional connectivity were not a result of altered blood flow but secondary to changes in either blood volume or metabolic activity." Given the explanations offered for the observed increases in functional connectivity, what could that mean clinically?</li></ol>
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<b>REVIEWER</b>	Cesar Fernandez-de-las-Peñas Universidad Rey Juan Carlos
<b>REVIEW RETURNED</b>	18-Aug-2018

<b>GENERAL COMMENTS</b>	<p>This paper covers a huge and relevant topic of discussion which deserves publication; however, there are several comments that need to be addressed</p> <p>Introduction: I am not sure if authors should report to chiropractic manipulation. I think that the risk is related to cervical manipulation in general, unless the authors have used a particular chiropractic technique. I think that a broad discussion of spinal manipulation should be considered. In addition, authors should clarify that vertebral artery risk is related to upper cervical spine manipulation and not just to cervical spine manipulation. An hypothesis is welcome at the end of introduction. For instance, did the authors expected a decrease in blood flow in the homo-lateral or contra-lateral side of the manipulation.</p> <p>Methods: in the study design there is a typo. Case should be deleted. In the study design it should be clarified that all participants received both interventions in the opposite order. It is not clear in the current version of the manuscript. In the inclusion criteria it seems that patients were WAD associated neck pain and not mechanical. This should be clearly stated in the text. Some figures of the interventions would be helpful for readers. In addition, it should be clarified if the cervical spine manipulation was applied to the mid or upper cervical spine. It is not clear in the text.</p> <p>Results: The main problem of this study is the huge number of patients excluded from the initial screening. More data about the reasons for exclusion should be provided. This section is poorly written since there is no statistical analysis included in the text. This should be included.</p> <p>Table 1: there is mention to NRS headache when headache was an exclusion criteria.</p>
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<b>REVIEWER</b>	Peter Lee P.N.Lee Statistics and Computing Ltd. Sutton, Surrey, United Kingdom
<b>REVIEW RETURNED</b>	07-Nov-2018

<b>GENERAL COMMENTS</b>	<p>The authors describe the results of a case-crossover design in which randomization divided 20 participants into two sequences of interventions; maximal neck rotation (MNR) followed by cervical manipulation (CM) or CM followed by MNR. Measurements of vertebral artery and cerebral haemodynamics were made before either intervention, and then following each intervention.</p> <p>The whole point of carrying out a case-crossover study is to compare responses within patient. Thus one would have expected to find assessments of MNR-Neutral and of FM-Neutral differences. However, all that is presented in Tables 2 and 3 are</p>
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	<p>means and SDs for each manoeuvre, which are essentially irrelevant. Means and SDs of the differences are what one needs to see. It is totally possible, for example, to have a small but consistent difference between the test manoeuvres that would not become evident from the results as presented.</p> <p>No results are presented by sequence of intervention either. Given the design of the study divided participants in this way, it would seem logical to present some results comparing the two groups. If sequence of intervention is important, might it not matter that testing of the neutral neck position was always tested first? A design in which only one intervention is considered with participants allocated to the different sequences of neutral and intervention might be better.</p> <p>The study is claimed to have “insured control of confounders”. But the analyses cannot be controlled for sequence of testing, as measurements using the neutral test manoeuvre always came first.</p> <p>In the paragraph concerning sample size, the assumption that “a change of at least 2 SD from the normal mean flow would be clinically meaningful”. But clinical meaningfulness has absolutely nothing to do with variability in response.</p>
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### VERSION 1 – AUTHOR RESPONSE

REVIEWER 1:

Comment	Response
Page 8, lines 6-12: The 4 sentences included in this section appear to be repeated in the following paragraph (Page 8, lines 14-20).	Thank you very much for your comments. You are correct, we inadvertently duplicated the noted 4 sentences. We have deleted the repeated sentences.
Page 8, lines 9-12: In discussing the changes in BOLD signals, the authors offer the following explanation: “However, when examining the aforementioned areas specifically for changes in blood flow using ASL, no significant changes were observed between any of the test head conditions. This strongly suggests that the observed increased functional connectivity were not a result of altered blood flow but secondary to changes in either blood volume or metabolic activity.” Given the explanations offered for the observed increases in functional connectivity, what could that mean clinically?	We thank the reviewer for their thoughtful comment. The areas found in our study with increased functional connectivity on BOLD have been previously cited as being involved with the functions of visually guided eye movements (1), fascial and word recognition (2), visuospatial processing (3), episodic memory, reflection upon self and consciousness (4). Engagement of these functions appear to be consistent with the sensory inputs and self-awareness in subjects in our study from handling of a body region such as the neck. We offer a possible clinical explanation, which can be found on Pg. 9 lines 7-11.

1. Heinen SJ. 1996 Ex Brain Res. The function of the cerebellar uvula in monkey during optokinetic and pursuit eye movements: single-unit responses and lesion effects.
2. Kanwisher N, Yovel G. The fusiform face area: a cortical region specialized for the perception of faces. Philos Trans R Soc Lond B Biol Sci. 2006 Dec 29;361(1476):2109-28

3. Lamm C, Windischberger C, Leodolter U, Moser E, Bauer H. Evidence for premotor cortex activity during dynamic visuospatial imagery from single-trial functional magnetic resonance imaging and event-related slow cortical potentials. *Neuroimage*. 2001 Aug;14(2):268-83.
4. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. 2006 Mar;129(Pt 3):564-83. Epub 2006 Jan 6.

REVIEWER 2:

Comment	Response
<p>I am not sure if authors should report to chiropractic manipulation. I think that the risk is related to cervical manipulation in general, unless the authors have used a particular chiropractic technique. I think that a broad discussion of spinal manipulation should be considered. In addition, authors should clarify that vertebral artery risk is related to upper cervical spine manipulation and not just to cervical spine manipulation.</p>	<p>We appreciate the reviewer's comment and agree that generic description is appropriate. We have removed the word chiropractic proceeding manipulation. We also added additional wording related to relevance of spinal manipulation in neck pain and the upper cervical spine (page 3, lines 20-21, lines 26-27), in addition to the previous content related to the presumed relationship of cervical manipulation and blood flow.</p>
<p>An hypothesis is welcome at the end of introduction. For instance, did the authors expected a decrease in blood flow in the homo-lateral or contra-lateral side of the manipulation.</p>	<p>Thank you for your suggested edit. We have added our hypothesis to the end of the introduction (page 3, lines 42 to 45).</p>
<p>in the study design there is a typo. Case should be deleted.</p>	<p>We agree with the reviewer's suggestion and have deleted the word "case" from our design description.</p>
<p>In the study design it should be clarified that all participants received both interventions in the opposite order. It is not clear in the current version of the manuscript.</p>	<p>We have edited the description of our study design to more clearly describe our procedures (page 3, lines 51 and 52). We also edited our procedure to clarify the order of procedures (See page 4, lines 39-40, 45-46 and 52).</p>
<p>In the inclusion criteria it seems that patients were WAD associated neck pain and not mechanical. This should be clearly stated in the text. Some figures of the interventions would be helpful for readers.</p>	<p>Thank you for your helpful suggestion. We have added a sentence in the participant section (page 4, lines 8 and 9) in order to help clarify that both mechanical neck pain and neck pain from a whiplash associated disorder were included.</p>
<p>In addition, it should be clarified if the cervical spine manipulation was applied to the mid or upper cervical spine. It is not clear in the text.</p>	<p>The authors thank the reviewer for their comment. We have added several clarifying statements (page 4, line 26) in the randomization and masking as well as procedure sections (page 4, line 52) in order to clarify that the manipulative procedure was targeted to C1-2.</p>

Comment	Response
The main problem of this study is the huge number of patients excluded from the initial screening. More data about the reasons for exclusion should be provided.	Further clarification for participant exclusions can be found on Pg. 7, lines 5-9.
This section is poorly written since there is no statistical analysis included in the text. This should be included.	We appreciate the reviewer's comment and have added further description of our results. These can be found on page 7, lines 28-35 and lines 48-53.
Table 1: there is mention to NRS headache when headache was an exclusion criteria.	We thank the reviewer for their question. Although correct in stating that headaches were an exclusion criteria; however, for participants to be excluded they were required to have been suffering from severe headaches (defined as >6/10 in intensity). This statement can be found on page 4, line 17 and 18 in the participants section.

REVIEWER 3:

Comment	Response
<p>The authors describe the results of a case-crossover design in which randomization divided 20 participants into two sequences of interventions; maximal neck rotation (MNR) followed by cervical manipulation (CM) or CM followed by MNR. Measurements of vertebral artery and cerebral haemodynamics were made before either intervention, and then following each intervention.</p> <p>The whole point of carrying out a case-crossover study is to compare responses within patient. Thus one would have expected to find assessments of MNR-Neutral and of FM-Neutral differences. However, all that is presented in Tables 2 and 3 are means and SDs for each manoeuvre, which are essentially irrelevant. Means and SDs of the differences are what one needs to see. It is totally possible, for example, to have a small but consistent difference between the test manoeuvres that would not become evident from the results as presented.</p> <p>No results are presented by sequence of intervention either. Given the design of the study divided participants in this way, it would seem logical to present some results comparing the two groups.</p>	<p>The authors thank the reviewer for their insightful comment. As reported in the methods we utilized a repeated measures one-way ANOVA and a two-way ANOVA in order to compare the procedures to the baseline measure (please see pg 6, lines 46-49 and lines 54-56). As a result of re-analysis, we have added content in the results (pg 7, lines 28-35) and updated Table 2 and Table 3. We have also included the mean differences as requested to clarify changes found between baseline and procedures (Table 4). In addition, we've added analysis on the impact of procedure order as found on pg 7, lines 48-53, as well as Table 5.</p>

Comment	Response
If sequence of intervention is important, might it not matter that testing of the neutral neck position was always tested first? A design in which only one intervention is considered with participants allocated to the different sequences of neutral and intervention might be better.	The authors thank the reviewer for their comment. Our primary aim was to determine whether cervical manipulation led to a clinically meaningful change in vertebral and cerebral hemodynamics compared to neutral neck position or neck rotation in adult patients with chronic neck pain. As such, we conducted a crossover trial in order to avoid sequencing effect and used neutral as the baseline measure from which to compare changes in position or manipulation. It is our opinion that neutral head position is not needed to be tested as an intervention given this position is assumed to be theoretically least challenging to the arterial structures.
The study is claimed to have “insured control of confounders”. But the analyses cannot be controlled for sequence of testing, as measurements using the neutral test manoeuvre always came first.	The authors thank the reviewer for their comment. We understand that the reviewer is concerned with order bias which is different from confounding. Neutral position was the initial intervention as it served as our baseline and therefore was required to be performed initially in all participants. We have added analysis on ordering effect in order to help satisfy concerns (Table 5).
In the paragraph concerning sample size, the assumption that “a change of at least 2 SD from the normal mean flow would be clinically meaningful”. But clinical meaningfulness has absolutely nothing to do with variability in response.	The authors thank the reviewer for their comment. As stated, no study has provided information on cerebral perfusion and blood flow following mechanical challenges to the neck and thus we were required to assume a statistically significant change from normal hemodynamics. A change of 2SD (proposed important effect size) from the mean was selected and suggested that any value greater would be a significant variability in blood flow or perfusion. <sup>1</sup> We have changed wording of the sentence in hopes to clarify (page 6, line 9-13).

1. Cohen J. Statistical power analysis for the behavioral sciences 2nd ed. New Jersey: Lawrence Erlbaum Associates, Publishers, 1988.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Peter Lee P.N.Lee Statistics and Computing Ltd. Sutton, Surrey, UK
<b>REVIEW RETURNED</b>	21-Jan-2019

<b>GENERAL COMMENTS</b>	The authors have answered all the questions I raised regarding the statistics, and the additional results are fine.
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	The only trivial point I had was that in Table 2, I wondered why the authors presented the upper 95% confidence limit before the lower one, when it is usual to present them the other way round.
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