PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Acupuncture for chronic neck pain with sensitive points: study protocol for a multicenter randomized controlled trial
AUTHORS	Sun, Mingsheng; Geng, Guoyan; Chen, Jiao; Ma, Xingsha; Yan, Mingxi; Liu, Xiaojia; Du, Jiarong; Cai, Dingjun; Zheng, Hui; Zhao, Ling; Liang, Fan-rong

VERSION 1 - REVIEW

REVIEWER	Ben Colagiuri University of Sydney, Australia
REVIEW RETURNED	29-Nov-2018

GENERAL COMMENTS	This protocol details a planned large-scale RCT of sensitised-point acupuncture for chronic neck pain. The study proposed has two major strengths. The first is the inclusion of both a sham-control group and a wait-list control group. This is critical for determining the factors that influence treatment responses following acupuncture, i.e. whether it is the specific stimulation of the theorised acupoints or the generic treatment processes involved in the procedures (e.g. that elicit placebo effects). The second is the large sample size, with the authors appropriately noting that many previous trials of acupuncture suffer from low power. Thus, this is an important study that will provide useful data on the efficacy of acupuncture for chronic neck pain and should serve as a good example of a useful design for unpacking the components that may contribute to improvement following acupuncture, i.e. the specific acupuncture effects, the placebo effect, Hawthorne effects, regression to the mean, spontaneous recovery. There are some aspects that need to be clarified before publication can be recommended. In order of appearance, they are: - the abstract should make clear what highly sensitised acupoints are - Page 4: it was unclear why a limitation would be that low/non-sensitized acupoints being effect would cofound the study…isn't the key question whether it matters that sensitised points are used or not? - Page 4: "Although clinical trials have demonstrated that…" perhaps 'demonstrated' should be replaced with 'suggested' given the limitations to the previous work the authors discuss later in the paragraph - Page 5: given its relevance, more discussion of acupoint sensitisation and the supposed superior efficacy of treatment at these points is warranted - Page 6: will individuals be allowed to concurrently use acupuncture or other treatments (both non-pharmacological or pharmacological)? - Page 6: it is unclear what 'inspector' means

	- Page 6: please provide specific details of the stratification and block randomisation. - Page 6: be very specific about who will be blind, e.g. will assessors be blind? - Page 7 (and abstract): why are absolute values used in the PPT? - Page 9: are the sham points matched in terms of proximity to the source of pain relative to the other two groups? If not, could this introduce bias in terms of credibility? - Page 9: do all acupuncture groups get the PPT test? If not this could introduce bias between the active and sham groups due to additional attention/credibility. - Page 10: specify wording of the VAS question, i.e. is it overall pain or specifically neck pain. - Page 11: are all 5 follow-up points necessary? Could this overload patients? - Page 12: would a difference of 5 out of 100 VAS between high and low sensitised points be clinically meaningful? - Page 12: the data analysis plan is not sufficiently specified. What are the actual statistical tests that are planned? What will be the criteria for including covariates? Etc - Page 13: it was unclear what “enable the diagnostic component of the study to be maintained” meant - Page 13: another strength which should be discussed is having the sham group in terms of being able to understand contribution of placebo effect/expectancies. (See Colagiuri and Smith, 2010, eCAM). - Page 14: as above, it is unclear why low-sensitised acupoints being effective is a limitation.

REVIEWER	Anita Gross McMaster University Canada
REVIEW RETURNED	07-Feb-2019

GENERAL COMMENTS	Clarification and details of the methods are needed as follows: ABSTRACT 1. The research question should include all elements of PICOST (population, intervention, comparison, outcome, study design, timelines). Currently the P, I, partial O and partial S are defined. All outcomes categories should be noted. The comparisons (placebo and wait list) should be noted. The type of RCT should be explicitly stated (i.e. parallel group design). Key timeliness of the data reporting should be noted (i.e. at post treatment 4 weeks, 24 weeks). 2. There should be some reporting of planned statistical analysis methods, sample size determination, and serious adverse event recording INTRODUCTION Minor: 1. Express percentages as whole number (i.e. 64.52% round to 65%). 2. In the first paragraph (line 20 to 38), the "Burdon of Illness" is well presented. Add in one statement of direct cost estimate to society. with reference would strengthen this section. 3. update systematic review reference beyond 2009. (i.e. The American Journal of Chinese MedicineVol. 45, No. 08, pp. 1573-1595 (2017) No Access Effectiveness of Acupuncture and Electroacupuncture for Chronic

	Neck Pain: A Systematic Review and Meta-Analysis) METHODS AND ANALYSIS 1. The psychometric properties of outcomes (i.e. VAS) should be referenced. The minimal clinical important difference should be noted for the primary and key secondary outcomes. Perhaps insert an additional table that outlines the psychometric properties. I noticed that you do discuss this under sample size calculation but it also needs to appear in the methods section under outcomes.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. the abstract should make clear what highly sensitised acupoints are

Response: Highly sensitized acupoints are acupuncture points that are more sensitive than sensitized acupoints. Highly sensitized acupoints have a very marked change in the pain threshold or body temperature in the local area compared with common sensitized acupoints and unsensitized acupoints. We identified these highly sensitized acupoints based on objective measurements of the pain threshold and body temperature. The five points with the highest scores were defined as highly sensitized acupoints, while the rest were defined as sensitized acupoints.

We have further explained the concept of a 'sensitized acupoint' in the manuscript as follows (page 3, line 3): "According to the theory of traditional Chinese medicine, acupoints and tender points may become sensitized when the body is in a diseased state; stimulation of such sensitive points may lead to disease improvement and improved clinical efficacy".

2. Page 4: it was unclear why a limitation would be that low/non-sensitized acupoints being effect would cofound the study…isn't the key question whether it matters that sensitised points are used or not?

Response: We rephrased this sentence as follows (page 4, line 5): "There are several types of point sensitization, such as pain and heat. However, in the present trial, we only quantified pain as an indicator of sensitization, which might overlook the other forms of sensitization and not fully address the complexity of acupoint sensitization."

3. Page 4: "Although clinical trials have demonstrated that…" perhaps 'demonstrated' should be replaced with 'suggested' given the limitations to the previous work the authors discuss later in the paragraph

Response: We agree with this point, and have revised the sentence as suggested (page 4, line 22).

4. Page 5: given its relevance, more discussion of acupoint sensitisation and the supposed superior efficacy of treatment at these points is warranted

Response: We have revised the Discussion section as follows (page 5, line 4): “Clinical studies have confirmed that the sensitivity (PPT) at acupoints changes when patients are in a diseased state, such as shoulder pain (Yan, et al. 2017), knee osteoarthritis (Luo, et al. 2018), primary dysmenorrhea (Chen, et al. 2015), and premenstrual syndrome (Chae, et al. 2007). The degree of change in the PPT may objectively reflect the intensity of acupoint sensitization, and may be related to the disease status (Tunks, et al. 1988). Clinical studies have found that performing acupuncture at sensitive points achieves a superior effect (Zhang, et al. 2010; Chen and Kang. 2006). However, these studies did not quantify the sensitivity of points, which undermines the validity of the results. Consequently, the improvement in clinical efficacy may not have been optimized. Clinical trials have recently investigated the efficacy of acupuncture at objectively evaluated sensitive points (Tang, et al. 2018). This will further reveal the relationship between sensitive points and improved clinical efficacy. However, no study has yet focused on the efficacy of acupuncture at quantified sensitive points for the treatment of chronic neck pain. Therefore, we herein describe the protocol for an RCT that aims to evaluate the efficacy of acupuncture at sensitive points (acupoints or tender points) in relieving neck pain and improving cervical vertebral function and quality of life.”

5. Page 6: will individuals be allowed to concurrently use acupuncture or other treatments (both non-pharmacological or pharmacological)?

Response: If any participants experience severe neck pain during the initial 24 weeks, they will be permitted to take prescribed analgesic medications (such as non-steroidal anti-inflammatory drugs) or effective analgesic medications that they are accustomed to taking, and the details will be recorded on the Case Report Form. Sustained-release or prophylactic analgesics are not allowed. We have stated this information on page 10, line 6.

6. Page 6: it is unclear what ‘inspector’ means

Response: To make our meaning clearer, we replaced ‘inspector’ with ‘research assistant (RA)’ (page 6, line 22). The RA will be responsible for baseline evaluation, PPT measurement, and randomization.

7. Page 6: please provide specific details of the stratification and block randomisation.

Response: We added “Patients will be randomized in blocks of varying size within each site, stratified by sex and course of disease” on page 6, line 28.

8. Page 6: be very specific about who will be blind, e.g. will assessors be blind?

Response: We rewrote this sentence (page 7, line 6) as follows: “The patients receiving acupuncture treatment during the trial period, RA who performs the baseline assessment, acupuncturists, assessors, and statisticians will all be blinded.”

9. Page 7 (and abstract): why are absolute values used in the PPT?

Response: According to TCM theory, an increased or decreased pain threshold in comparison with healthy people is abnormal. All these points have been identified as the best points for acupuncture treatment. Therefore, we adopted the absolute values in the PPT calculation of sensitive points.

10. Page 9: are the sham points matched in terms of proximity to the source of pain relative to the other two groups? If not, could this introduce bias in terms of credibility?

Response: Most of the sham points were matched in terms of proximity to the source of pain relative to the other two groups. Furthermore, the same sham points were used in our previous research, which indicated that they provided a valid placebo.

• Zhao L, Chen J, Li Y, et al. The Long-term Effect of Acupuncture for Migraine Prophylaxis: A Randomized Clinical Trial[J]. Jama Internal Medicine, 2017, 177(4):508.

11. Page 9: do all acupuncture groups get the PPT test? If not this could introduce bias between the active and sham groups due to additional attention/credibility.

Response: All acupuncture groups will undergo the same PPT test.

12. Page 10: specify wording of the VAS question, i.e. is it overall pain or specifically neck pain.

Response: We rewrote this sentence (page 10, line 16): “The primary outcome will be the change in the VAS score for neck pain from baseline to 4 weeks.”

13. Page 11: are all 5 follow-up points necessary? Could this overload patients?

Response: Chronic neck pain is prone to recurrence, and so long-term follow-up helps to address whether acupuncture has a long-term therapeutic effect. We also considered the potential overload of the patients. To prevent this, we streamlined the follow-up process (via internet or telephone) to make it easier for patients. Our previous research has enabled us to gained experience in such follow-up, during which we formed a good mechanism of communication with patients. We will use the same communication protocol in this trial.

• Zhao L, Chen J, Li Y, et al. The Long-term Effect of Acupuncture for Migraine Prophylaxis: A Randomized Clinical Trial[J]. Jama Internal Medicine, 2017, 177(4):508.

14. Page 12: would a difference of 5 out of 100 VAS between high and low sensitised points be clinically meaningful?

Response: There are currently no data on the minimal detectable change and minimal clinically important difference for pain severity in patients with chronic neck pain. Furthermore, the clinical difference between acupoint versus placebo (which is 6.3 out of 100 on the VAS according to a previous study) is only considered a statistically significant difference (Basiouni A. Acupuncture versus placebo for the treatment of chronic mechanical neck pain: a randomized, controlled trial. Annals of internal medicine 2004;141(12):911). Therefore, we consider that a difference of 5 out of 100 on the VAS between high and low sensitized acupoints would be sufficient to address our hypothesis. However, the significance of this difference in pain from a clinical perspective remains uncertain. We will also address the magnitude of the clinical meaningfulness using other instruments, such as the Northwick Park Neck Pain Questionnaire, the McGill Pain Questionnaire, and the need for analgesic drugs.

15. Page 12: the data analysis plan is not sufficiently specified. What are the actual statistical tests that are planned? What will be the criteria for including covariates? Etc

Response: We rewrote this paragraph (page 13, line 10): “A statistician blinded to the group allocations will conduct all analyses using the SAS version 9.4 software package (SAS Institute Inc., Cary, NC, USA). First, the basic information of the four groups will be described, including patient characteristics, medical characteristics, outcome variables, and adverse events. If an adjustment is needed for a baseline value that differs between groups, covariance analysis will be performed. Data will be presented as mean (SD) for continuous variables, and as frequency (percentage) for categorical variables. Group comparisons will then be undertaken using $\chi 2$ tests for categorical characteristics, and analysis of variance for continuous variables. The primary analyses will examine whether acupuncture performed in the highly-sensitive acupoints group achieves statistically better treatment outcomes (pain, quality of life, neck function, and emotional disorders) than acupuncture in the low/non-sensitive acupoints group, sham acupuncture group, and waiting-list control group. To accommodate the correlation between repeated measures from the same participant, generalized linear models with random effects will be fitted to assess the effect of the intervention on outcome variables over time, while accounting for the effects of potential confounders (e.g., age, sex, analgesic medications, and other treatments). We will use the last value carried forward method to impute missing data for the primary and secondary outcomes. All analyses will use two-sided tests, and a p value of less than 0.05 will be considered statistically significant.”

16. Page 13: it was unclear what “enable the diagnostic component of the study to be maintained” meant

Response: We deleted “enable the diagnostic component of the study to be maintained”.

17. Page 13: another strength which should be discussed is having the sham group in terms of being able to understand contribution of placebo effect/expectancies. (See Colagiuri and Smith, 2010, eCAM).

Response: We added the following sentence (page 14, line 12): “In contrast with previous studies (Tang, et al. 2018), this trial established a sham group to investigate the placebo effect of acupuncture.”

18. Page 14: as above, it is unclear why low-sensitised acupoints being effective is a limitation.

Response: We rewrote this paragraph as follows (page 14, line 21): “As this will be the first study to investigate the effectiveness of acupuncture at sensitive acupoints for chronic neck pain, this RCT may have some limitations. There are several types of point sensitization, such as pain and heat (Ben, et al. 2012; Chen, et al. 2011). However, in this trial, we only quantified pain as the indicator of sensitization, which might overlook the other forms of acupoint sensitization. Further study is needed to confirm the improvement in the clinical efficacy of acupuncture at different kinds of sensitive acupoints. If the results show that acupuncture therapy at sensitive acupoints is safe and effective in reducing chronic neck pain, this study will provide evidence to support the superior clinical efficacy of performing acupuncture at sensitive acupoints compared with low/non-sensitive acupoints.”

Responses to the comments from Reviewer 2

Comments

ABSTRACT

1. The research question should include all elements of PICOST (population, intervention, comparison, outcome, study design, timelines). Currently the P, I, partial O and partial S are defined. All outcomes categories should be noted. The comparisons (placebo and wait list) should be noted. The type of RCT should be explicitly stated (i.e. parallel group design). Key timeliness of the data reporting should be noted (i.e. at post treatment 4 weeks, 24 weeks).

Response: We rewrote the abstract in accordance with your suggestions as follows (page 3, line 9): “This multicenter, randomized, sham and waitlist controlled, explanatory, and parallel clinical trial will include 716 patients with chronic neck pain” and “before treatment, post-treatment, and 4, 8, 12, 16, and 20 weeks post-treatment”.

2. There should be some reporting of planned statistical analysis methods, sample size determination, and serious adverse event recording

Response: We rewrote this section in accordance with your suggestions as follows (page 3, line 12): “The primary outcome will be the change in the visual analogue scale pain score from baseline to 4 weeks. Secondary outcomes will be the Northwick Park Neck Pain Questionnaire and McGill pain questionnaire, 12-item Short-Form health survey, Neck Disability Index, changes in the pressure pain threshold, range of cervical motion, Self-Rating Anxiety Scale, Self-Rating Depression Scale, and adverse events before treatment, post-treatment, and 4, 8, 12, 16, and 20 weeks post-treatment. The intention-to-treat approach will be used in the statistical analysis. Group comparisons will be undertaken using $\chi 2$ tests for categorical characteristics, and analysis of variance for continuous variables to analyze whether acupuncture in the highly-sensitive acupoints group achieves better treatment outcomes than in each of the other three groups.”

INTRODUCTION

3. Express percentages as whole number (i.e. 64.52% round to 65%).

Response: We rewrote this percentage as a whole number (page 4, line 13).

4. In the first paragraph (line 20 to 38), the "Burdon of Illness" is well presented. Add in one statement of direct cost estimate to society. with reference would strengthen this section.

Response: We added “The mean annual total costs accrued by each patient with neck pain in the USA are $8,512, which is 182% higher than the costs accrued by the general population”, and added a reference to support this information (Kleinman N, Patel AA, Benson C, et al. Economic burden of back and neck pain: effect of a neuropathic component. Popul Health Manag 2014;17(4):224-32 doi: 10.1089/pop.2013.0071). Please see the revised section on page 4, line 16.

5. update systematic review reference beyond 2009. (i.e. The American Journal of Chinese MedicineVol. 45, No. 08, pp. 1573-1595 (2017) No Access

Effectiveness of Acupuncture and Electroacupuncture for Chronic Neck Pain: A Systematic Review and Meta-Analysis)

Response: We updated this systematic review reference (page 4, line 28).

METHODS AND ANALYSIS

6. The psychometric properties of outcomes (i.e. VAS) should be referenced. The minimal clinical important difference should be noted for the primary and key secondary outcomes. Perhaps insert an additional table that outlines the psychometric properties. I noticed that you do discuss this under sample size calculation but it also needs to appear in the methods section under outcomes.

Response: We added the following information:

“The VAS is considered a valid method with which to assess pain intensity in clinical trials (Caraceni, et al. 2002). The strengths of the VAS are its ease of use, good reliability and validity, and metric measure that enables parametric testing. However, its limitation is that it is difficult for some subjects to mentally transform a subjective sensation into a mark on a straight line. Furthermore, previous research has suggested that the validity of VAS estimates performed by patients with chronic pain may be unsatisfactory (Carlsson. 1983).”

“We will also use the following indicators to comprehensively evaluate pain. The intensity of neck pain will be measured using the Northwick Park Neck Pain Questionnaire and the McGill Pain Questionnaire. The changes in the PPT during the treatment phase will be evaluated. The times and doses of analgesic drugs taken during the study period, and the disease-related treatment performed during the follow-up period will also be recorded.”

Please see the relevant revisions on page 10, line 18.