PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Identification of the optimal points for the acupuncture treatment of neck pain in China: protocol for a multicenter, matched, case-control study
AUTHORS	Sun, Mingsheng; Tao, Siyuan; Geng, Guoyan; Peng, Jieru; Ma, Xingsha; Yan, Mingxi; Chen, Jiao; Cai, Dingjun; Zheng, Hui; Yang, Chunxia; Zhao, Ling; Liang, Fan-rong

VERSION 1 - REVIEW

REVIEWER	Fabiano Politti Nove de Julho University - Brazil
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	General comments The study is interesting and has clinical application. However, it needs important tweaks so that it can be run. The description of the diagnosis and the classification of patients is poor. It is important to make clear in the study the classification (e.g: Neck pain with mobility déficits, Neck pain with movement coordination impairments....) and phase (acute, subacute or chronic). Please consult and follow the guidelines of Blanpied et al., 2017 (J Orthop Sports Phys Ther. 2017; 47 (7): A1-A83. Doi: 10.2519 / jospt.2017.0302). These details should be clear in the Study Methods. Specific comments Title: It would be interesting to include the word "multicenter study" in the title of the manuscript. Abstract - Introduction: Very long. I suggest that it be reduced - Methods: hypothesis is weak, I suggest review. Include statistical analysis. Introduction "English must be checked. For example, in paragraph 1 the word "neck pain" appears 5 times. This makes the text tiring. - Include a hypothesis and a convincing clinical contribution to the study. Methods

	Page 31 .... In the sentence: "Our previous small sample-sized study indicated that the rate of acupoint sensitization ranged from" lack the indication of the bibliographical reference " Statistical analysis. The form used for the calculation of the sample is not clear. Perhaps this should be reviewed and calculated from the characteristics of the population.

REVIEWER	Jianhua Liu Traditional Chinese medicine hospital of Guangdong province
REVIEW RETURNED	13-Feb-2019

GENERAL COMMENTS	— p.7, 35-38. Will the study use independent outcome assessors and statisticians? This seems important. — p.11, 35-38.If using case-control studies, odds ratios should be calculated in the statistics analysis, which usually approximate to the relative risk. — please explain why choose the case control study and not using the cross section study?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. It is important to make clear in the study the classification (e.g: Neck pain with mobility déficits, Neck pain with movement coordination impairments....) and phase (acute, subacute or chronic). Please consult and follow the guidelines of Blanpied et al., 2017 (J Orthop Sports Phys Ther. 2017; 47 (7): A1-A83. Doi: 10.2519 / jospt.2017.0302). These details should be clear in the Study Methods.

Response: We rewrote the inclusion criteria of Patients in accordance with your suggestions as follows (page 4, line 30): “(1) have nontraumatic neck pain with mobility deficits in the acute and chronic stages”.

Title:

2. It would be interesting to include the word "multicenter study" in the title of the manuscript.

Response: We agree with this point, and have revised the title with your suggestions as follows: “Identification of the optimal points for the acupuncture treatment of neck pain in China: protocol for a multicenter, matched, case-control study”.

Abstract

3. Introduction: Very long. I suggest that it be reduced

Response: We rewrote the abstract in accordance with your suggestions as follows (page 2, line 2): “Neck pain (NP) is a common condition that can be effectively treated by acupuncture. However, various treatment points prescription (such as local acupoints, distal acupoints, and sensitized acupoints) could be used. The present study aims to identify the types of sensitization and distribution of sensitized points in patients with NP, to analyze the cutoff values and sensitization rate for acupoint sensitization in patients, and to summarize the dominant forms of optimal sensitized points in patients. This information will be helpful in the choice of optimal points for the treatment of NP.”.

4. Methods: hypothesis is weak, I suggest review. Include statistical analysis.

Response: We rewrote the abstract in accordance with your suggestions as follows (page 2, line 9): “This multicenter, matched, case-control study will enroll 224 patients with NP, and 224 age- and sex-matched healthy subjects for control. Body surface temperature, mechanical pain threshold, pressure pain threshold, and skin resistance will be assessed at the 15 acupoints most frequently used to treat NP, and at the five body regions in which pain most frequently occurs. We believe that in the state of disease, the sensitive points occurs with high frequency, and the sensitive points of different sensitizations will overlap, and the final optimal points from overlap may be closely related to the selection of clinical treatment points. Hypothesis testing will be used to compare the differences in variables between cases and controls. In addition, receiver operating characteristic curve analysis will be used to explore the cutoff values of the sensitive states of heat, pain, and electrical resistance that indicate sensitization of the acupoint. The optimal points will be comprehensively determined by the acupoint sensitization rate and OR value.”.

Introduction

5. "English must be checked. For example, in paragraph 1 the word "neck pain" appears 5 times. This makes the text tiring.

Response: We rewrote the introduction in accordance with your suggestions as follows (page 3, line 5): “Neck pain (NP) is a common clinical condition often accompanied by tenderness at sensitive points. The global lifetime prevalence of NP was 48.5% in 2006. (Fejer, et al. 2006) The prevalence of white-collar workers in China was 33.9-54.8% in 2016 and has an increase tendency in recent years, (Anhui Medical Journal. 2017) imposing considerable personal and socioeconomic burdens. Muscle relaxants and non-steroidal anti-inflammatory drugs are used to treat this disease, however, such medications carry a risk of adverse effects, and neither drug is better than non-pharmacological alternative treatments. (Fejer, et al. 2006)”.

6. Include a hypothesis and a convincing clinical contribution to the study.

Response: We rewrote the introduction in accordance with your suggestions as follows (page 4, line 1): “Herein, we describe the protocol for an observational study that aims to identify the different types of sensitization (e.g. temperature, tenderness) and the distribution of sensitized acupoints in patients with NP, to analyze the cutoff values for acupoint sensitization in patients with NP, and to determine the most optimal sensitization types seen at sensitized points in patients with NP. We believe that in the state of disease, the sensitive points occurs with high frequency (manifested as changes in temperature, pain threshold etc), and the sensitive points of different sensitizations will overlap, and the final optimal points from overlap may be closely related to the selection of clinical treatment points. Previous small sample studies have confirmed the feasibility of sensitization testing. (Luo, et al. 2018) The present study will provide a basis for the selection of the optimal treatment points for NP in clinical practice.”

Methods

7. Page 31 .... In the sentence: "Our previous small sample-sized study indicated that the rate of acupoint sensitization ranged from" lack the indication of the bibliographical reference "

Response: We rewrote this sentence and added the bibliographical reference on page 9, line 22.

• Chen R, Kang M. Acupoint Heat-Sensitization and Its Clinical Significance. Journal of Traditional Chinese Medicine 2006;2001(4):488-489

8. Statistical analysis. The form used for the calculation of the sample is not clear. Perhaps this should be reviewed and calculated from the characteristics of the population.

Response: Previous study indicated that the rate of acupoint sensitization in patients ranged from 20% to 70%, (Chen, et al. 2006) so we set this rate at 50% to calculate the minimum sample size required for the proposed study. With acupoint sensitization rate of 20% in healthy subjects, the odds ratio is 4. According to Chow’s formula in comparing two sample proportion, (Chow, et al. 2003) we assumed an α level of 0.05, a β of 0.01, thus, the smallest sample size is 408 with two-sided confidence and a ratio of control subjects to cases of 1 (TrialSize package in R software). Considering the potential non-response rate and sampling effectiveness as 10%, the final sample size is 448 (224 patients, plus 224 age- and sex-matched healthy subjects).

• Chow SC, Shao J, Wang H. Sample size calculations in clinical research. New York: Marcel Dekker, 2003.

• Operational Record of R Software：

```
> library(TrialSize)

> f<-TwoSampleProportion.Equality(0.05,0.01,0.5,0.2,4,0.2)

> f

[1] 408.7874
```

Responses to the comments from Reviewer 2

Comments

1. p.7, 35-38. Will the study use independent outcome assessors and statisticians? This seems important.

Response: We agree with this point, and rewrote this sentence “The statistical data evaluation will be independently performed by the West China School of Public Health at Sichuan University, China.” on page 10, line 5.

2. p.11, 35-38. If using case-control studies, odds ratios should be calculated in the statistics analysis, which usually approximate to the relative risk.

Response: We added “Meanwhile, OR represents the ratio of acupoint sensitization of patients and healthy subjects. Therefore, this study combines OR and sensitization rate of all acupoints to find out the optimal points in each sensitization.” on page 10, line 21.

3. Please explain why choose the case control study and not using the cross section study?

Response: This study aims to find out the differences of acupoints sensitization between patients with neck pain and healthy subjects for further analysis which can be achieved by both cross-sectional study and case-control study. But in the pre-test, it took about two hours to complete a subject's acupoints test, if we use cross-sectional method, it will increase the time cost of sample collection and decrease the feasibility. Therefore, we use case-control study in this research.

VERSION 2 – REVIEW

REVIEWER	Fabiano Politti Nove de Julho University - Brasil
REVIEW RETURNED	01-Apr-2019

GENERAL COMMENTS	The authors did a good job of revising the text. In the abstract item, page 2, line 39, it is necessary to leave the abbreviation "OR".

REVIEWER	Jianhua Liu The Secondary Medical College, Guangzhou University of Traditional Chinese Medicine
REVIEW RETURNED	17-Apr-2019

GENERAL COMMENTS	The authors have made a very diligent effort to revise based on the previous comments, and the paper is much improved. I have two suggestions for minor changes, listed below. — It's not necessary to mention that ”We believe that in the state of disease, the sensitive points…” in the Methods and analysis of abstract. The study methods only need the objective descriptions. — This study as a case-control study to investigate the association between the acupoint sensitization and neck pain in a relatively large population. The last paragraph of introduction refers to “We believe that in the state of disease, the sensitive points occurs with high frequency …, and the final optimal points from overlap may be closely related to...”, so the optimal acupoints in this study just as a deduction or inference. Except for conducting a randomized controlled trial, my suggestion is that the present study couldn't identify the optimal acupoints for neck pain treatment (only provide evidence for the selection of acupoints)

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

In the abstract item, page 2, line 39, it is necessary to leave the abbreviation "OR".

Response: We have revised the abstract with your suggestions as follows: “The optimal points will be comprehensively determined by the acupoint sensitization rate and odds ratio (OR) value.” on page 2, line 37.

Reviewer: 2

1. It's not necessary to mention that “We believe that in the state of disease, the sensitive points…” in the Methods and analysis of abstract. The study methods only need the objective descriptions.

Response: We agree with this point, and deleted this sentence “We believe that in the state of disease, the sensitive points occurs with high frequency, and the sensitive points of different

sensitizations will overlap, and the final optimal points from overlap may be closely related to the selection of clinical treatment points." on page 2, line 33.

2. This study as a case-control study to investigate the association between the acupoint sensitization and neck pain in a relatively large population.

The last paragraph of introduction refers to "We believe that in the state of disease, the sensitive points occurs with high frequency …, and the final optimal points from overlap may be closely related to...", so the optimal acupoints in this study just as a deduction or inference. Except for conducting a randomized controlled trial, my suggestion is that the present study couldn't identify the optimal acupoints for neck pain treatment (only provide evidence for the selection of acupoints)

Response: We agree with this point, and have revised this sentence "The present study will provide evidence for the selection of the optimal treatment points for NP in clinical practice." on page 4, line 3.