PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Blinding assessment in randomized sham-controlled trials of acupuncture: protocol for a systematic survey

Authors

Yang, Jiahui; Liu, Jiali; Luo, Xiaochao; Yao, Minghong; Fu, Yong; Li, Ling; Sun, Xin

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Liu, Jian-Ping**
Affiliation	**Beijing University of Chinese Medicine, Centre for Evidence-Based Chinese Medicine**
Date	**30-Sep-2024**
COI	**None**

The topic is very interesting and relecvant for future clinical trials in acupuncutre. Like placebo control study, use of blinding is important, but whether the blinding is successul or not needs to be evaluated. I have following suggestions.

1. Since the procedure details in acupuncture treatment is important to evaluate the blinding, it would be important to extract data around the reporting standard of acupuncture, that is, STRICTA. So, the components of the reporting would be relevant to the assessment.

2. When analysing the data, especially on blinding success and effect size, it should be clear that the condition limited to pain, while for the whole trials searching, there is no limitatoin on disease or conditions.

3. The subject of blinding would be important, such as participants, or outcome assessors, this can be analysed based on subgroups.

Reviewer	**2**
Name	**Ma, Fuqiang**

Affiliation The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology

Date 10-Nov-2024

COI None

The objective of this paper is to examine the blind effectiveness of various fake acupuncture techniques and their impact on the efficacy estimation in randomized controlled trials (RCTs) of acupuncture, which holds significant clinical and scientific value. While the design concept of this study is well-defined and its objectives are clear, certain details and methodologies require further refinement.

1. Background knowledge: Although the introduction succinctly outlines the application of fake acupuncture techniques within RCTs, it would be beneficial to elaborate on the different types of fake acupuncture methods along with their respective advantages and disadvantages to enhance readers' understanding of the background and necessity for this research.

2. Literature review: It is advisable to incorporate recent references from relevant literature to strengthen the rationale behind the research question while elucidating existing studies' limitations in this field.

3. Methodology and analysis section: When employing Pearson's correlation coefficient to assess the relationship between blinded effectiveness and trial effect size, was variable distribution considered? If normality assumptions are not met, will non-parametric tests be employed as a supplementary analytical approach?

4. Adequacy of meta-regression analysis: Although it was indicated that meta-regression would be utilized to explore relationships, additional details were lacking. What potential confounding variables will be accounted for? How will these variables be integrated into the analytical model to ensure robust results?

5. Despite utilizing a quantitative approach for calculating effect sizes, how will variations in participants' baseline characteristics be addressed regarding their potential influence on outcomes?

6. The study states that an unprecedented number of sham acupuncture control trials will be included; however, does such a strategy effectively mitigate biases stemming from suboptimal study designs? Are there classifications established for summarizing and analyzing trials based on quality?

7. Given that this investigation aims to evaluate correlations between blind success rates and effect sizes, what are your perspectives on both applicability and limitations concerning different measures of blind success across various studies?

VERSION 1 - AUTHOR RESPONSE

Reviewer #1:

1. Since the procedure details in acupuncture treatment is important to evaluate the blinding, it would be important to extract data around the reporting standard of acupuncture, that is, STRICTA. So, the components of the reporting would be relevant to the assessment.

[Response] Thank you for your suggestion. We fully agree that the details of the acupuncture treatment process are crucial for assessing blinding. In the data extraction section, we have added more detailed content to the original acupuncture treatment data based on STRICTA, including the number of needle insertions per subject per session, names or location of points used, and the response sought. The updated content is as below.

Characteristics of acupuncture treatment

"We will record the characteristics of acupuncture treatment according to the STRICTA guideline(19). Including the rationale or theory of acupuncture, type of acupuncture (manual acupuncture, electroacupuncture), number of needle insertions per subject per session (mean and range), names or location of points used, acupoint prescription (standardized point prescription, partially individualized prescription, fully individualized prescription), depth of insertion, response sought (de qi, muscle twitch response, other, not reported), needle retention time, frequency and duration of treatment, total treatment sessions, needle type (diameter, length)…"

2. When analyzing the data, especially on blinding success and effect size, it should be clear that the condition limited to pain, while for the whole trials searching, there is no limitation on disease or conditions.

[Response] Thank you for your suggestion. We acknowledge the necessity of clearly defining the scope of our analysis. We have provided a more detailed explanation in the manuscript, explicitly stating that the relationship between blinding effectiveness and effect sizes is limited on trials involving pain-related disorders. The specifics are as below.

Eligibility criteria

"…This systematic survey has no disease or condition restriction, but for investigating the relationship between blinding effectiveness and trial effect sizes, this analysis will be limited on trials involving pain-related disorders."

Outcomes

"To evaluate the relationship between blinding effectiveness and trial effect sizes, we will use

the pain outcomes from acupuncture for chronic pain trials (e.g., neck pain, shoulder pain, low back pain, osteoarthritis pain). We will record the name of pain outcome, mean and standard deviation (SD) of changes from baseline pain intensity, and number of patients included for analyses in each treatment group."

3. The subject of blinding would be important, such as participants, or outcome assessors, this can be analyzed based on subgroups.

[Response] Thank you for your suggestion. We have added the relevant information to the manuscript, as below.

"We will conduct several subgroup analyses to investigate heterogeneity when sufficient data are available, such as based on the type of disease, type of acupuncture, type of sham acupuncture, patients' prior experience with acupuncture, subject of blinding."

Reviewer #2:

1. Background knowledge: Although the introduction succinctly outlines the application of fake acupuncture techniques within RCTs, it would be beneficial to elaborate on the different types of fake acupuncture methods along with their respective advantages and disadvantages to enhance readers' understanding of the background and necessity for this research.

[Response] Thank you for your suggestion. We have added the advantages and disadvantages of different types of sham acupuncture in introduction section, as below.

INTRODUCTION

"... To achieve blinding, various types of sham acupuncture have been used in trials, such as inserting needles at non-acupuncture points or with minimal penetration to mimic the physical sensation of needling, which can potentially induce a therapeutic effect, as well as using non-penetrating placebo devices like Streitberger and Park sham needle, which may not fully achieve patient blinding (11).

The effectiveness of binding of these sham acupuncture in acupuncture trials remains a topic of debate, with some studies suggesting that participants can still distinguish between real and sham acupuncture…"

2. Literature review: It is advisable to incorporate recent references from relevant literature to strengthen the rationale behind the research question while elucidating existing studies'

limitations in this field.

[Response] Thank you for your suggestion. We have supplemented the background by incorporating new references in introduction section, as below.

"…An earlier survey, including published literature up to 2011, evaluated the blinding effectiveness of acupuncture trials using a blinding index and found that 61% of participants maintained ideal blinding(13). Moreover, insufficient attention has been given to assessing and reporting blinding in practice. Several studies have shown that the success of blinding was assessed or reported in less than 10% of trials(4, 14), and methods for evaluating blinding were inconsistent and questionable(15); however, these results consisted mainly of trials in other fields of medicine, with only a few involving acupuncture trials. Additionally, a recent study proposed an exploratory principle and protocol for the blinding assessment without practical validation(16). Although these efforts, it remains unclear in practice how many sham-controlled acupuncture trials report blinding assessment, what methods are used to eval…"

3. Methodology and analysis section: When employing Pearson's correlation coefficient to assess the relationship between blinded effectiveness and trial effect size, was variable distribution considered? If normality assumptions are not met, will non-parametric tests be employed as a supplementary analytical approach?

[Response] Thank you for your suggestion. We will use Pearson's r correlation coefficient to assess the relationship between blinding effectiveness and trial effect sizes when the data meet the assumptions of normality and linearity. Otherwise, we will consider using non-parametric tests, such as Spearman's rank correlation coefficient. We have added and revised related information in the abstract and Methods and analysis section, as below.

Abstract

*"**Methods and analysis** …We will use Pearson's r correlation coefficient to assess the relationship between blinding effectiveness and trial effect sizes when variable distributions meet the assumptions of normality and linearity; otherwise, we will consider employing non-parametric tests…"*

Statistical analysis

"We will calculate the treatment effect using Hedges'g, a standardized mean difference (SMD), with its 95% confidence interval (CI)(22). We will use Pearson's r correlation coefficient to assess the relationship between blinding effectiveness and trial effect sizes when variable

distributions meet the assumptions of normality and linearity; otherwise, we will consider employing non-parametric tests, such as Spearman's rank correlation coefficient…"

4. Adequacy of meta-regression analysis: Although it was indicated that meta-regression would be utilized to explore relationships, additional details were lacking. What potential confounding variables will be accounted for? How will these variables be integrated into the analytical model to ensure robust results?

[Response] Thank you for your suggestion. We have supplemented this study with data on several confounding variables and have included these variables as covariates in the random-effects meta-regression model. The detailed information as below.

Statistical analysis

"…When sufficient data are available, we will also use meta-regression to explore the relationship while accounting for several potential confounding variables, such as the type of sham acupuncture, type of sham acupoints, insertion depth, needle stimulation, and patient' prior experience with acupuncture. These variables will be incorporated as covariates within a random-effects model to accommodate inter-study heterogeneity and account for intra-study variability…"

5. Despite utilizing a quantitative approach for calculating effect sizes, how will variations in participants' baseline characteristics be addressed regarding their potential influence on outcomes?

[Response] Thank you for your suggestion. We fully acknowledge that variations in patients' baseline characteristics may affect outcomes. One objective of our study is to investigate the relationship between blinding effectiveness and trial effect sizes, the study focus aligns with this concern. We will adjust for potential confounding variables, such as the type of sham acupuncture, type of sham acupoints, by including them as covariates in a random-effects meta-regression model, aiming to explore potential factors influencing this relationship. However, due to variability or lack of detailed data on patients characteristics in each included study, it is challenging to further explore the impact of differences in baseline characteristic on the relationship between blinding effectiveness and effect sizes. We have discussed this as a limitation, as below.

Strengths and limitations

"…Third, although we will use SMD to combine pain intensity data from different chronic pain disorders, there may still be heterogeneity between studies, such as variations in patient

baseline characteristics, which may have compromised our findings…"

6. The study states that an unprecedented number of sham acupuncture control trials will be included; However, does such a strategy effectively mitigate biases stemming from suboptimal study designs? Are there classifications established for summarizing and analyzing trials based on quality?

[Response] Thank you for your suggestion. The aims of this study are: (1) to investigate the proportion and study characteristics of sham-controlled trials reporting on blinding assessment, (2) to assess the blinding effectiveness of different types of sham acupuncture, (3) to investigate the relationship between blinding effectiveness and effect sizes in acupuncture RCTs. The strengths of our study lie in the rigorous review process, the use of standardized forms and calibration exercises to ensure consistency, and the incorporation of broad eligibility criteria to enhance generalizability. These methodological strengths enable us to address a series of unanswered questions that have not been adequately explored in prior research, rather than solely relying on a larger sample size. While the quality assessment of RCTs is significant, considering the nature of acupuncture intervention and sham acupuncture, as well as our objectives, we are inclined to believe that a detailed analysis based on RCT quality may not be strictly necessary, therefore, we do not design a classification established for summarizing and analyzing trials based on quality.

7. Given that this investigation aims to evaluate correlations between blind success rates and effect sizes, what are your perspectives on both applicability and limitations concerning different measures of blind success across various studies?

[Response] Thank you for your suggestion. One objective of our study is to investigate the relationship between blinding effectiveness and trial effect sizes. In practice, there may be different methods to measure the success of blinding in practice, with guessing treatment allocation commonly used, and we will assess the blinding effectiveness of different types of sham acupuncture based on this data, which may ignore data from other methods. We have made relevant discussions in the limitation of discussion section, as below.

Strengths and limitations

"…Second, there may be different methods to measure the success of blinding in practice. Guessing treatment allocation is a commonly used measurement method by researchers, and we will assess the blinding effectiveness of different types of sham acupuncture based on this

measurement data. This may ignore data from other methods, but we will extract and describe the results of other blind measurements."

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Ma, Fuqiang**
Affiliation	**The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology**
Date	**04-Dec-2024**
COI	

This is an interesting study, recommended for publication.