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Acupuncture for headache in COVID-19
A protocol for systematic review and meta-analysis

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease which making people difficult to breathe and often accompanied with headache. Acupuncture have been proved the therapeutic effect on headache, but there has been no high-quality evidence on acupuncture for the headache in COVID-19. This study is designed to evaluate the effectiveness and safety of acupuncture for headache in COVID-19.

Methods: Randomized controlled trials from December 2019 to July 2021 will be included without restrictions on language or publication date. PubMed, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Databases, China National Knowledge Infrastructure, Wanfang database, and VIP database will be searched. Two researchers will independently select studies, extract data and evaluate study quality. Cochrane risk of bias tool for randomized trials will be used to assess the risk of bias of included studies. Statistical analyses will be performed using the Review Manager V.5.3 and stata 14.0.

Ethics and dissemination: This study will not involve personal information. Ethical approval will not be required. We will publish the results in a peer-reviewed journal.

PROSPERO Trial registration number: CRD42021270722

Abbreviations: COVID-19 = coronavirus disease 2019, PRISMA-P = preferred reporting items for systematic reviews and meta-analysis protocol, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: acupuncture, coronavirus disease 2019, headache, protocol

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with high infectivity and tall mortality, and it has rapidly developed into a worldwide public health emergencies in the world. The novel coronavirus pneumonia patients not only show respiratory symptoms such as dyspnea, but also have nervous system symptoms such as headache and dizziness.[1,2] Research has indicated that headache is one of the most common neurologic symptoms, with a prevalence of about 10%.[3–5] The National Institutes of Health noted that headache is one of the common symptoms of postacute sequelae of SARS-CoV-2 infection.[6] Meanwhile, according to the latest report, headache is the most common symptoms for delta variant cases. Headache may be worsen or start after major stressful life events or posttraumatic stress disorder. Nowadays, the treatment methods for headache of COVID-19 are mainly western medicines which may prolong viral replication in SARS-CoV2 and might be associated with a worse COVID-19 clinical course.[7] Therefore, alleviate the headache in COVID-19 patients is helpful to improve the quality of life.

Acupuncture is one of the external treatments in Traditional Chinese Medicine with a history of more than 3000 years. Studies have proved that acupuncture has unique advantages in the treatment of headache and was widely used in worldwide.[8–10] During the COVID-19 epidemic, acupuncture has been used as a complementary treatment for COVID-19 in China and has been confirmed the efficacy of COVID-19 with routine regimens.[11]

It has been demonstrated that dopamine along with its D1 and D2 receptors participates in electroacupuncture-induced analgesia and lung immunity might be shaped by dopamine receptors.[12] Differing from the opioids and other medicines, which may exacerbate the symptoms of gastrointestinal disorders, acupuncture may be a safe and effective method for pain management in COVID-19 patients.[12,13]

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As of yet, there has been no high-quality evidence on acupuncture for the headache in COVID-19. Therefore, we designed this study to better understanding of the effectiveness and safety of acupuncture therapy for headache in COVID-19.

2. Methods

2.1. Study registration

This systematic review protocol has been registered in the PROSPERO (No. CRD42021270722). We will follow recommendations outlined in The Cochrane Handbook of Systematic Review of Interventions and the preferred reporting items for systematic reviews and meta-analysis protocol (PRISMA-P) statement guidelines. If amendments are needed, we will update our protocol to include any changes in the whole process of research.

2.2. Types of studies

Randomized controlled trails will be included, without restrictions on language or publication date.

2.3. Types of participants

Subjects with documented COVID-19 with headache of 4 weeks duration or longer. There is no restrictions on gender, race, and disease stage. Patients with history of headache prior to COVID-19 infection will be excluded.

2.4. Types of interventions and comparisons

In addition to the treatment of COVID-19, treatment group interventions comprised acupuncture, electro-acupuncture, auricular acupuncture, or laser acupuncture, and comparator groups intervention: comfort therapy (placebo, pseudo-acupuncture or blank control), other therapies (Western medicine, usual care or nondrug therapy, etc).

2.5. Types of outcomes

Outcomes include effectiveness indicators and safety indicators.

2.5.1. Effectiveness indicators. Clinical variables will be set as the effectiveness indicators, such as the headache frequency, headache intensity, duration of headache, times of using painkiller, and quality of life.

2.5.2. Safety indicator. The incidence of adverse events.

2.6. Search methods for identification of studies

Randomized controlled trials will be extracted from PubMed, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Databases, China National Knowledge Infrastructure, Wanfang database, and VIP database. The complete PubMed search strategy is summarized in Table 1.

2.7. Data collection

2.7.1. Selection of studies. Two reviewers (MS and JX) will search the study independently, and then they will screen the studies by reviewing titles and abstracts or full text if necessary. Further unresolved discrepancy was managed by a third reviewer (MXZ). The selection process is summarized using PRISMA flow diagram. Details of the selection procedure for studies are shown in a PRISMA flow chart (Fig. 1).

2.7.2. Data extraction and management. Data will then be extracted from the selected studies by 2 reviewers (WJJ and CXZ). The detailed extraction information are as follows: basic information of the included studies, baseline characteristics of the subjects, intervention measures and control measures, key elements of bias risk assessment, outcome indicators, etc. Any disagreements will be resolved by discussion, or by consultation with a third author (XMZ).

Endnote X9.3 will be used to manage the search results and perform screening and the duplicate publications will be excluded.

2.7.3. Quality and bias assessment. The methodological quality and risk of bias of each trial will be assessed by 2 review authors (JYB and CXZ) independently according to the Cochrane Handbook. The following characteristics will be assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Based on the assessments of the studies against these 7 domains, they will be classified as being of "low risk", "high risk", or "unclear risk" of bias. Any disagreements will be resolved by discussion, or by consultation with another reviewer (XMZ).

2.7.4. Dealing with missing data. If complete literature or relevant data is not available, we will contact the corresponding author. However, if the missing data cannot be obtained, then the study will be excluded from the analysis.

2.8. Statistical analysis

2.8.1. Measures of treatment effect. Review Manager (RevMan 5.3) software will be used to conduct this meta-analysis.

Table 1

PubMed search strategy.

| Number	Search items
#1	"covid 19"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "coronavirus disease 19"[Title/Abstract] OR "2019 novel coronavirus"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "disease 2019 coronavirus"[Title/Abstract] OR "sars coronavirus 2 infection"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract]
#2	"acupuncture"[Title/Abstract] OR "moxibustion"[Title/Abstract] OR "electroacupuncture"[Title/Abstract] OR "fire needle"[Title/Abstract] OR "acupoint injection"[Title/Abstract] OR "auricular point"[Title/Abstract] OR "warming needle moxibustion"[Title/Abstract]
#3	"Headaches"[Title/Abstract] OR "Head"[Title/Abstract] OR "Cephalodynia"[Title/Abstract] OR "Cranial"[Title/Abstract] OR "Cephalalgia"[Title/Abstract] OR "Cephalgia"[Title/Abstract]
#4	#1 and #2 and #3
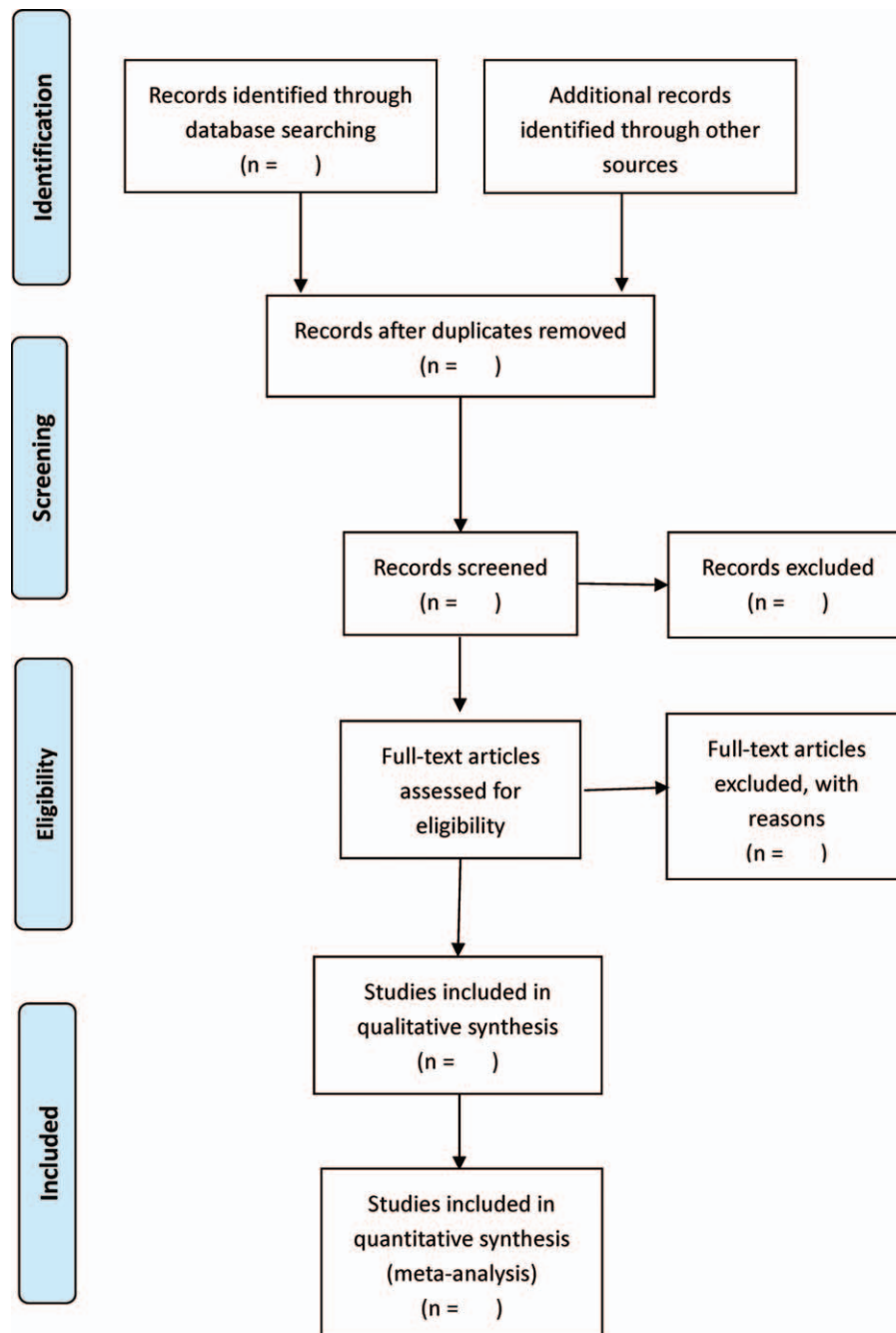
Figure 1. PRISMA flow diagram. PRISMA = preferred reporting items for systematic reviews and meta-analysis.

Dichotomous outcomes will be presented as risk ratios with 95% confidence intervals. When continuous outcomes exists, mean differences or standardized mean differences will be calculated.

2.8.2. Assessment of heterogeneity. The choice of whether to conduct a meta-analysis and which model to use (fixed or random effects) will depend on the level of statistical heterogeneity assessed by the P value and I^2 index. $P < .05$ considered to represent significant statistical heterogeneity, and $I^2 > 50\%$ considered to be indicative of substantial heterogeneity.

2.8.3. Data synthesis. The fixed effect model will be used if no significant heterogeneity is observed; otherwise, the random effect model will be applied for statistical analysis.[14]

2.8.4. Subgroup analysis. According to the results of the data synthesis, we will perform subgroup analyses, or a meta-regression to analyze the source of any heterogeneity.

2.8.5. Assessment of reporting bias. When outcomes include more than 10 studies, we will use Stata 14.0 to access the reporting bias by funnel plot and Egger test.[15]

2.8.6. Sensitivity analysis. Sensitivity analyses will be performed to determine whether the results are affected by leave1out with Stata14.0.

2.8.7. Quality of evidence evaluation. The evidence quality will be evaluated by 2 viewers (MS and JX) independently with the grading of recommendations assessment, development and evaluation. According to 5 parameters (publication bias, indirectness, inconsistency, imprecision, and study limitations), evidence quality will be rated "high", "moderate'," "low" according to the rating standards.

2.8.8. Ethics and dissemination. Since this study does not involve the patient privacy, ethical approval is not required. Our research results will be shared and shown through conference reports and peer-reviewed journals.

3. Discussion

COVID-19 caused by SARS-CoV-2, which has become a serious public health threat worldwide, with millions of people at risk in increasing countries.[16] Dyspnea, fatigue, fever and cough were highly prevalent in COVID-19, however, the COVID-19 pandemic has brought numerous patients complaining of neurologic manifestations, such as headache and dizziness.[17–19] Headache can lead to worsening symptoms, and intensification of negative emotions.[20]

Acupuncture was regarded as a complementary technique, and was widely applied in treating headache. Acupuncture is convenient, simple, and low in cost. It is benefit for COVID-19 patients with headache to accept acupuncture treatment. Thus, this study aimed to provide evidence of acupuncture therapy for headache in COVID-19 and aided treatment decisions.

Author contributions

Conceptualization: Mi Sun.
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Writing – review & editing: Qiwen Tan.

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