INPLASY PROTOCOL

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None declared.

Efficacy and Safety Evaluation of Electro-acupuncture in the Treatment of Patients with Migraine: A Protocol of Systematic Review and Network Meta-Analysis

Dong, Z[1]; Li, L[2]; Liu, H[3]; Zhang, H[4]; Zhou, X[5]; Fu, Y[6].

Review question / Objective: **The Global Burden of Disease Research Survey released by Lancet Neurol shows that migraine is the sixth most common disease. Calculated according to the number of healthy life years lost by disability, migraine is the second disabling disease and the fifth disabling disease in China. Electro-acupuncture(EA) is a modern method of acupuncture that posseses the characteristics of safety, effectiveness, and fewer adverse reactions. It has also been internationally accepted as one of several complementary and alternative medical therapies for migraine, which is often recommended at the beginning of outbreak and in those with moderate degrees of headache to achieve more favorable effects. Recently researches have demonstrated that EA can effectively reduce the degree and frequency of headache, relieve the accompanying symptoms, and holds the advantage of little side effects. Although previous systematic reviews have shown that EA is safer and more effective compared with Western medicine, it has been included in the literature for a long time. The author's preliminary search found that a large number of randomized controlled trials(RCT) research results have been published in last decade, and considering the heavy burden of migraine, it is substantially imperious to renew outdated clinical evidence supporting EA in the treatment of patients with migraine. This protocol is developed to conduct a systematic review and network meta-analysis to evaluate the evidences related to the effectiveness and safety of EA on migraine, and to provide a basis for the development of reliable clinical strategies for patients with migraine.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 August 2021 and was last updated on 14 August 2021 (registration number INPLASY202180058).

INTRODUCTION

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disability, migraine is the second disabling disease and the fifth disabling disease in China. Electro-acupuncture(EA) is a modern method of acupuncture that posseses the characteristics of safety, effectiveness, and fewer adverse reactions. It has also been internationally accepted as one of several complementary and alternative medical therapies for migraine, which is often recommended at the beginning of outbreak and in those with moderate degrees of headache to achieve more favorable effects. Recently researches have demonstrated that EA can effectively reduce the degree and frequency of headache, relieve the accompanying symptoms, and holds the advantage of little side effects. Although previous systematic reviews have shown that EA is safer and more effective compared with Western medicine, it has been included in the literature for a long time. The author's preliminary search found that a large number of randomized controlled trials(RCT) research results have been published in last decade, and considering the heavy burden of migraine, it is substantially imperious to renew outdated clinical evidence supporting EA in the treatment of patients with migraine. This protocol is developed to conduct a systematic review and network meta-analysis to evaluate the evidences related to the effectiveness and safety of EA on migraine, and to provide a basis for the development of reliable clinical strategies for patients with migraine.

Rationale: Migraine is a common neurological disorder, but there is no satisfactory intervention. Acupuncture has been shown to reduce migraine attacks in the short term. EA is a CAM therapy commonly used to treat migraine.Some studies have suggested that EA is an effective treatment for poststroke spasticity, knee osteoarthritis, tinnitus, and Obesity. As a form of acupuncture, EA can effectively reduce the degree and frequency of headache, relieve the accompanying symptoms, and holds the advantage of little side effects. However, there has been little systematic review showing the evidences of the effectiveness and safety of EA on migraine over the years, let alone the quantitative comparative network meta-analysis efficacy and safety. Thus, it is substantially imperious to take an overall consideration of both the efficacy and the safety of EA and renew outdated clinical evidence supporting EA in the treatment of patients with migraine.

Condition being studied: Migraine is a common primary headache, and its condition is characterized by recurrent, severe headache with pulsating on one or both sides, and it mostly occurs on the side of the head. The disease is more onset than in children and adolescence. It reaches the peak of incidence in young and middle-aged. It is more common in women. The ratio of male to female is around 1:3. According to ICHD-III (International Classification of Headache Disorders, 3rd edition beta version), patients with migraine has two major subtypes, migraine without or with aura. Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Moreover, migraine can also lead to cognitive decline, asymptomatic cerebral infarction of the posterior circulation, and white matter lesions. The high incidence and disability rate of migraine seriously affect the physical and mental health and quality of life of patients, and bring a heavy economic burden to the family and society. In terms of treatment, most studies believe that the disease cannot be cured, but measures can be taken to control symptoms. Western medicine treats the disease, and the acute phase drug treatment usually chooses "stratified method" or "step method" to quickly and continuously relieve pain and reduce headache recurrence, such as non-specific analgesic paracetamol, specific analgesic triptan.However, some western medicines have adverse effects such as lethargy, increase in body weight, depression, and extrapyramidal symptoms, which lead to reduced patient compliance,

and the efficacy is often lower than expected. Acupuncture has been a widely used method to treat migraine in Asia and Western countries. electro-acupuncture (EA) is a modern way of administering acupuncture defined as the passage of a pulsed electric current through the body tissue via one (or more) pairs of acupuncture needles for therapeutic purpose.EA is known to be effective for persistent pain, neuropathic pain, and analgesia. Several systematic reviews of EA have been published. However, there has been no systematic review on the effectiveness of EA on migraine. Therefore, we preliminary search found that a large number of RCTs research results have been published in last decade and propose the current protocol to perform the systematic review by assessing the evidences related to the effectiveness of EA on patients with migraine.

METHODS

Search strategy: Eight English and Chinese medical databases, including PubMed, The Cochrane Library, Web of Science, EMBASE, the China National Knowledge Infrastructure (CNKI [Chinese]), Wanfang Data (Chinese), and Vip Data (Chinese), Chinese Biology Medicine(CBM [Chinese]) will be electronically searched from inception to 14th August 2021. A supplemental search of the gray literature will be performed in the library of jiangxi University of Chinese Medicine, and relevant systematic reviews will be also included and analyzed to supplement other potentially relevant literature. Non-full-text articles will be acquired through e-mail communication between the research team and the authors of these studies. Manually search authoritative journals of acupuncture and moxibustion (such as Chin Acup Moxib) to supplement the documents not included in the databases. The searching terms to be used will include migraine, headache, and hemicrania. We will also search the terms electro-acupuncture as well as acupuncture, acupuncture therapy, acupuncture, acupuncture analgesia and acupuncture points for extensive searches. The following example search strategy will be used for PubMed:(("migraine disorders"[MeSH] OR "headache"[Title/Abstract] OR "hemicrania"[Title/Abstract]) AND ("acupuncture"[MeSH] OR "acupuncture therapy"[MeSH] OR "acupuncture-moxibustion"[Title/Abstract] OR "acupuncture therapy"[Title/Abstract] OR "electroacupuncture"[Title/Abstract] OR "acupuncture combined with"[Title/Abstract] OR "acusector"[Title/Abstract] OR "quick puncture"[Title/Abstract] OR "needling"[Title/Abstract]) AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract])) NOT ("animals"[MeSH] NOT "humans"[MeSH]) .The above search strategy will be modified and used for the other databases.

Participant or population: Patients with diagnosed migraine will be included. The diagnostic criteria are the International Classification of Headache Disorders or its equivalent. Patients with migraine with or without aura and other special types will be included. There are no restrictions on age, sex, course of disease, degree of illness, as well as source of cases for patients with diagnosed migraine.

Intervention: In case of the combination with other treatments, the intervention will be limited to EA and transcutaneous electrical acupoint stimulation, which are must based on theory of Traditional Chinese Medicine or Acupuncture (meridians and acupoints) combined with the electrical stimulation of the instrument to treat patients with migraine.

Comparator: The control group will be included individuals who underwent treatment with routine Western medicine, sham-EA, blank control, manual acupuncture, and acupoint catgut embedding. We will investigate the following comparisons: 1. The experimental group and the control group each had

routine nursing, and the effect was evaluated either with or without acupuncture intervention; 2. EA and related therapies are only compared to placebo or sham treatment; 3. EA and related therapies plus active treatment methods or drugs, compared with placebo or sham treatment plus active treatment methods or drugs.

Study designs to be included: In order to maintain rigorous objectivity and reliability, the systematic review and network meta-analysis will include RCTs including quasirandomized controlled trials (quasi-RCTs). We will exclude any types of studies such as controlled (non-randomized) clinical trials (CCTs), cohort studies, case sees, and case reports.

Eligibility criteria: Studies will be included so long as inclusion criteria are met. The eligibility criteria are summarized using the princi of PICOS(patients/participants, intervention, comparisons/control, outcomes, and study design type). Exclusion criteria are as follows: semi-randomized design; secondary migraine studies, such as those addressing subarachnoid hemorrhage, cerebral thrombosis, hypertension, and arteritis; EA application guided by non-TCM theory; EA combined with other therapies as the intervention in the experimental group; control group including Chinese herbal medicine or other Chinese patent medicine(s), medications not recommended by the guideline, or combined with acupuncture.

Information sources: Eight English and Chinese medical databases, including PubMed, The Cochrane Library, Web of Science, EMBASE, the China National Knowledge Infrastructure (CNKI [Chinese]), Wanfang Data (Chinese), and Vip Data (Chinese), Chinese Biology Medicine(CBM [Chinese]) will be electronically searched from inception to 14th August 2021. A supplemental search of the gray literature will be performed in the library of jiangxi University of Chinese Medicine, and relevant systematic reviews will be also included and analyzed to supplement other potentially relevant literature. We will also contact the investigators of these trials to ask for preliminary date if possible.To ensure literature saturation, we will manually search authoritative journals of acupuncture and moxibustion (such as Chin Acup Moxib) to supplement the documents not included in the databases.

Main outcome(s): The main outcomes will be the therapeutic effects of treatment on the Migraine. This will be headache pain intensity and the total treatment effective rate (i.e., the rate of healing, complete response, partial response, and no response). Headache pain intensity may be indicated on the visual analogue scale (VAS) or frequency of headache outbreak (times/month); The total treatment effective rate is the number of patients with improvement in the number of migraine attacks or of the migraine symptoms. This will show the effectiveness of EA.

Additional outcome(s): Additional outcomes will include the following measures: 1. Impact of migraine-related symptoms (headache frequency, headache duration time) as measured with validated questionnaires. 2. Migraine-associated symptoms (nausea, photophobia, phonophobia); 3. Quality of life: evaluated by general or migraine-specific scales 4. The occurrence of adverse events can be reported narratively by qualitative analysis.

Data management: The results of search will be exported to the EndNote (Clarivate Analytics, version 20) referencing software and duplicate studies will be removed using this software. The selection process will be performed by two authors (Z-WD and H-L) independently. Initially, we will screen and evaluation the titles and abstracts of studies, and select those likely to be of relevance to our systematic review. In the second stage of selection, we will assess the full-text of the studies and confirm the eligibility for our review. When there are any disagreements, we will resolve the disagreements by discussion. Using the PRISMA-compliant flow chart (http://www.prismastatement.org), this study screening and selection process will

be documented and summarized. The reasons for excluding studies will be provided in a flowchart. If the information in the included articles is incomplete or difficult to be judged during the screening process, the author(s) will be contacted. If it is difficult to receive a response from the original author, the missing information will be excluded. A third researcher(Prof. Y-F) will be consulted after discussion if there is disagreement during cross-correction. Regarding to data extraction, there will be two researchers(Z-WD and LH-L) independently extract data and establish a summary table, which will contain basic information regarding the research (e.g., title, author names and/or date of publication, and location of study); baseline information of the population (e.g., sample size, age, sex, and diagnosis); the experimental and control groups (such as the type, duration, frequency, and dose of intervention); and factors related to indictors of results, and the risk of bias (such as the method of randomization, concealment, blinding, and follow-up), it should be noted that a blinding method is difficult to perform in EA research. In other words, if the blinding method was only implemented among patients, the research is considered to involve low risk of bias for the implementation of the blinding method. The results will also be crosschecked in this process, and any disagreement between the results from the two researchers(Z-WD and LH-L) will be resolved after discussion and consultation with an arbiter (Prof. Y-F).

Quality assessment / Risk of bias analysis: To perform the quality assessment of the RCTs, we will use a data extraction form (Excel). The extraction form will be designed by all the authors in consensus. The data to be extracted will include the first author, year of publication, patient characteristics, intervention and comparison details, sample size and dropouts, outcomes and adverse events. The quality assessment will be performed using the "Risk of bias"' tool from the Cochrane Handbook V.5.3.0. The "Risk of bias" tool includes random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective reporting, and other sources of bias. It should be noted that a blinding method is difficult to perform in EA research. In other words, if the blinding method was only implemented among patients, the research is considered to involve low risk of bias for the implementation of the blinding method. Two researchers(Z-WD and LH-L) answered these questions with "yes", "unclear", or "no" to evaluate risk of bias. If an included study satisfied >4 items, it was grouped as low risk of bias; 1 to 4 items will be grouped as moderate risk of bias; and 0 or 1 item was grouped as high risk of bias. Disagreement during this procedure was resolved after discussion and consultation with a third researcher (Prof. X-Z). To assess the reporting biases, we will assess the publication bias with a funnel plot when a sufficient number of included studies (at least 10 trials) are available. We will also attempt to determine the possible reasons for any asymmetries in results, such as a selective outcome reporting bias, small-study effects, a poor methodology, or true heterogeneities in the included studies.

Strategy of data synthesis: We will do data analysis to compare the outcomes between the intervention and control groups. Data analysis will be performed with the values that measured at the end of the treatment period. When quantitative synthesis, we will analyze a single measurement of each outcome in each participant. Each participant's outcome measurement will be counted only once. The data synthesis will be performed with Rev Man V.5.3.0 for Windows.For continuous data, we will calculate the effect size of the interventions using the mean differences (MDs) with 95% CIs. If the trials present the outcome values on different scales, we will use the standard mean difference (SMD) with 95% CIs. Binary outcomes will be calculated as risk ratio (RR). We will calculate the data for the meta-analysis using fixed or random effects. If data synthesis is not applicable, we will use narrative analysis.In the network meta-analysis, three-arm studies will be separated into two arms for all

possible combinations, and Stata will be used to produce plots of the network meta-analysis for the comparison of each outcome measure. Data pertaining to the network meta-analysis will be analyzed using GeMTC 0.14.3, and Markov Chain Monte Carlo (MCMC) analysis was used to perform Bayesian inference with the consistency model. The software uses four chains for simulation and the number of iterations will be set to 50,000. The first 20,000 iterations will be used for annealing to eliminate the influence of the initial value, and the final 30,000 will be used for sampling. Estimation and inference will be made under the assumption that the MCMC analysis will reach a stable convergence state. The inconsistency model will be used to evaluate stability of the research results using the MCMC statistical model, and the parameters will be set using the same model. We will analyze three treatment outcomes at different time points separately (MMD, the frequency of migraine attacks and responder rates).

Subgroup analysis: To reduce the likelihood of spurious findings and avoid a false positive result, this systematic review will perform a subgroup analysis to explore and assess the heterogeneity. In cases of high heterogeneity, we will conduct subgroup analyses according to the subtypes of migraine (migraine with aura, migraine without aura), quality of study evidence (high risk, unclear and low risk), or to the other factors affecting the outcomes.

Sensitivity analysis: Sensitivity analysis will be performed to evaluate the stability and reliability of the combined results of the meta-analysis and also assesse whether the combined results are unduly affected by a single study. This procedure will be conducted using RevMan to eliminate individual studies one by one.

Language: Articles whose full text can be obtained will be included.Considering the language restriction of researchers, the included studies will be limited to the literature written in English or Chinese.

Country(ies) involved: The People's Republic of China.

Other relevant information: This systematic evaluation and network meta-analysis of EA for migraine will be based on the principles of the statement of PRISMA.The efficacy and safety of EA in migraine treatment will be evaluated based on multiple outcome measures. Nevertheless, this protocol may have some limitations. First of all, the inclusion is limited to the studies of Chinese and English. Secondly, different dosage of herbal medicine, age of patients and small sample size of trials may lead to some bias. At last but not least, whether the EA is consistent with baseline characteristics of the patients is an important consideration. Migraine with or without aura, the length of migraine history, the intensity of migraine, and the sample size of different studies can all influence outcomes. The qualifications and experience of the physicians and the characteristics of acupuncture vary widely, which could result in different effects including factors of acupoints, techniques, deqi, stimulation intensity, duration, needle specification, and frequency. To improve the reliability and acceptance of our study, we will publish this systematic review of EA in a peer-reviewed journal. If there are the major changes of this protocol, we will write the changes in the review. This study will form the basis to conduct additional research and provide evidence for the effectiveness of EA for migraine.

Keywords: Electro-acupuncture; Migraine; Systematic Review; Network Meta-Analysis; Protocol.

Dissemination plans: This systematic review and network meta-analysis will not need ethical approval, because it doesn't involve human beings. We will publish this systematic review and network meta-analysis electronically in a peer-reviewed journal. This systematic review and network meta-analysis will give healthcare practitioners good practical guide and information for treating migraine.

Contributions of each author:

Author 1 - Zhiwei Dong - ZD developed the search methods, performed data analysis, registered this protocol and drafted the original manuscript.

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Author 2 - Linhui Li - LL developed the search methods, performed data analysis, registered this protocol and drafted the original manuscript.ZD and LL contributed equally to this work and should be considered as co-first authors.

Author 3 - Hui Liu - The author examined the eligibility criteria in clinical practice and complete the research selection and assessment strategy of the risk of bias.

Author 4 - Haifeng Zhang - The author modified and revised the final version of this protocol.

Author 5 - Xu Zhou - The author read, provieded feedback and put forward valuable suggestions.

Author 6 - Yong Fu - The author is the guarantor of funding acquisition, corresponding author in this article, and will act as an arbitrator in the event of a disagreement. All authors have read and approved the final manuscript.