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Keywords:	Migraine Disorders, Acupuncture, Network Meta-Analysis, systematic review, protocol

Acupuncture methods for acute migraine attack: a Bayesian network meta-analysis protocol

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Abstract

Introduction Migraine is one of the main causes of disability worldwide particularly in young adult and middle-aged women, and drugs are the firstline treatment of acute migraine attack. However, drug overuse not only generates gastrointestinal and cardiovascular disorders but also brings the increased pain and frequent attacks. Multiple clinical trials and systematic reviews suggested acupuncture as an effective treatment for acute migraine attack but the methods were vary. We aim to rank the effectiveness of these methods to get a prioritization regimen.

Objective To compare the efficacy of all acupuncture methods with sham acupuncture and conventional medicine for the treatment of patients with acute migraine attack.

Methods Six databases will be searched including MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL),China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP) and Wanfang Database. The primary outcomes will be the pain intensity, the percentage of participants of a 50% reduction and the percentage of participants have headache-free at 2 hours after treatment.The secondary outcomes will include the adverse events to assess safety. Bayesian network meta-analyses will be conducted by WinBUGS1.4.3. Finally, we will use the Grading of Recommendations Assessment, Development and Evaluation System to assess the quality of evidence.

Ethics and dissemination The results will be disseminated through peer-reviewed

publication. Any private patient data will not be contained, threrfore, there is no ethical considerations associated with this protocol.

PROSPERO registration number CRD42019126472

Strengths and limitations of this study:

►This study will be the first network meta-analysis to compare various acupuncture methods for acute migraine using bayesian framework.

►The quality of evidence will be assessed by the Grading of Recommendations Assessment, Development and Evaluation System.

►Only Chinese and English databases will be retrieved and this may lead to the language bias.

Key words: Migraine Disorders; Acupuncture; Network Meta-Analysis; systematic review; protocol

Introduction:

Description of the condition

Migraine, a neurological disease characterized by recurrent attacks of unilateral location headache, pulsating quality,moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia[1].Untreated or unsuccessfully treated attacks can last 4-72 hours and brings a serious impact on the patients' quality of life. In accordance with the 2016 Global Burden of neurological disorders Study, migraine was one of the main causes of disability worldwide particularly in young adult and middle-aged women and it ranked as the second largest contributor of neurological disability-adjusted life-years(DALYs).

Although the cause of migraine remains unclear, it is now widely accepted that migraine with a strong genetic basis should be viewed as a complex brain network disorder involves multiple cortical, subcortical and brainstem regions.[2]. However, as the awareness of migraine increased, researchers always concerned about the prevention of attacks so that there have seen little progress in therapeutics that can effectively control symptoms. Triptans, ergotamine derivatives, NSAIDs and opioids are widely considered effective in treating acute migraine attack[3]. Nevertheless, the side effects of drug use should not be neglected.Not just gastrointestinal and cardiovascular disorders[4], the pain becomes increasingly worse when patients take painkillers or triptan drugs too frequently, that may get themselves into a vicious

cycle[5]. The side effects of substance abuse drive people to seek nonpharmacologic therapies so that developing alternative therapies that are safety and effectively for acute migraine attack is necessary.

Description of the intervention

Acupuncture is one of the main therapies in Traditional Chinese Medicine(TCM). It works by inserting needles into specific area on skin(acupoints) or along meridians at certain depth and produce a sensation of "De qi" simultaneously, which is often described as sour, numb radiating or distending pain. The sensation can be enhanced by electrical stimulation(electroacupuncture), heat(moxibustion acupuncture), or frequent manual stimulation(manual acupuncture) [6]and these foregoing methods are what we will investigate.

The philosophy behind TCM focuses on maneuvers to balance life energy but the mechanism is difficult to study[7]. Biochemical evidence shows that acupuncture increases the activity of the opioidergic system, releasing serotonin, dopamine, neurotrophins, and nitric oxide, which may be effective in treating disorders like migraine[8]. Although the mechanism is not that clear, acupuncture is still widely used in treating migraine. According to a survey in the USA,9.9% of patients who accepted acupuncture treatment had been treated for migraine or other headaches with acupuncture[9]. In recent years, controlled clinical trials on acute migraine have been increasing[10-12] and there were also several Cochrane systematic reviews confirmed the effectiveness and safety of acupuncture[13][14]. However, there has been little systematic review of acupuncture for acute migraine and previous systematic reviews have only considered evidence from comparison of acupuncture methods with medicine or sham acupuncture but have failed to assess the comparative efficacy of all acupuncture methods. Therefore, determining the best acupuncture methods for relieving pain is intractable. In the present study, we choose manual acupuncture, electroacupuncture,moxibustion acupuncture and sham acupuncture as the objects based on the theory of TCM and the needling instrument is not modified.

Objectives

- The objectives of this systematic review and network meta-analysis are: (1)to compare and rank all acupuncture methods in terms of efficacy in the treatment of migraine; (2)to produce a credible evidence of the comparison of acupuncture, sham acupuncture and conventional medicine for migraine. The outcomes will provide evidence for the current controversy of acupuncture and are expected to provide references for clinical practice and health policy decisions.

Methods:

This protocol will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement and Checklist of Items to Include When Reporting a Systematic Review Involving a Network

Meta-analysis[15][16] and has been registered on PROSPERO(CRD42019126472, supplementary file 1 for PRISMA-P checklist).

Eligibility criteria

Types of studies

Only randomized controlled trials (RCTs) published in English or Chinese will be included without any region restriction. The first period of randomised cross-over trials will be included. Literature reviews,animal studies, retrospective studies, case reports and studies of unavailable data will be excluded.

Types of participants

The participants of the studies were adults(>18 years) suffering from acute migraine according to the definition of the Headache Classification Subcommittee of the International Headache Society(a) or any other accepted diagnostic guidelines. Participants with migraines who had a definite cause such as intracranial lesions will be excluded.Gender or nationality will not be limited.

Types of intervention

In this protocol, acupuncture methods including traditional manual acupuncture(TA), electroacupuncture(EA), moxibustion acupuncture(MA, needle warming through moxibustion), a combination of any two of these methods or a combination of these acupuncture methods with conventional medicine(CM) regardless of acupoints selection or needling techniques. The duration will not be restricted. These methods are based on the theory of traditional Chinese medicine and the needling instrument is not modified. Therefore, dry needle, fire needle, laser acupuncture, bee venom acupuncture, acupotomy and irrelevant treatments such as blood letting therapy, cupping and herbal medicine will be excluded. Figure 1 illustrates the network plot of all possible direct comparisons.

Types of control groups

Different acupuncture method from treatment group, sham acupuncture(SA, intervention resembling verum acupuncture but the needle inserted superficial or at non-acupuncture points or the ‘paclebo’ needles not inserted into skin[17]), placebo, conventional medicine will be included. Trails comparing two acupoint selection or acupuncture manipulation will be excluded.

Types of outcome measures

Studies reporting one or more of the following outcomes will be included.

Primary outcomes

The objective of this review is to evaluate the analgesic effect of acupuncture methods for acute migraine attack. Hence the primary outcomes including the pain intensity and the percentage of participants of a 50% reduction of headache within 2 hours after treatment.

1.The pain intensity was measured by an acceptable headache scores such as a VAS, a numerical rating scale (NRS)[18] that were used at a time from the treatment finished to 2 hours. With studies presented multiple results in terms of time, the score at 2 hours or at the closest time to 2 hours that expost to therapy will be included.

2.The percentage of participants of a ⩾50% pain reduction at 2 hours after treatment.

3.The percentage of participants have headache-free at 2 hours after treatment[19].

Secondary outcome

The adverse events directly relating to the intervention will be reported to assess safety.

Search strategy

We will search the following electronic database:MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP) and Wanfang Database. Furthermore, we will search the clinical trail registries,dissertations, conference proceedings and grey literature to reduce publication bias. The references of reviews and meta-analysis will also be manually searched in case of omissions. The search dates will be from the inception of online databases until 25 February 2019 and languages will be limited to either English or Chinese. The retrieval mode will be a combination of free words and MeSH terms including Migraine Disorders, migraine, acupuncture therapy, acupuncture, electroacupuncture, moxibustion acupuncture.etc. The search strategy for PubMed is shown in table 1.

Table 1	Search strategy used for the PubMed database
No.	Search terms
1	randomized controlled trial [pt]
2	controlled clinical trial [pt]

3	randomized [tiab]
4	placebo [tiab]
5	clinical trials as topic [mesh: noexp]
6	randomly [ab]
7	trial [ti]
8	OR 1-7
9	animals [mh]
10	humans [mh]
11	9 NOT 10
12	8 NOT 11
13	Migraine Disorders[Mesh]
14	migraine
15	migrain*
16	OR 13-15
17	12 AND 16
18	acupuncture therapy[Mesh]
19	acupuncture treatment
20	pharmacoacupuncture treatment
21	pharmacoacupuncture therapy
22	acupuncture[Mesh]
23	electroacupuncture
24	moxibustion acupuncture
25	warming needle moxibustion
26	OR 18-25

27	17 AND 26

Study selection and data extraction

One reviewer will perform the searches according to the search strategy and download the citations. NoteExpress3.0 will be used to remove duplicates electronically and manually. Two reviewers will independently screen the study titles and abstracts and then retrieve the studies consistent with the eligibility for full-text. Any disagreement between reviewers will be resolved through discussion with a third reviewer. All trails will be allocated to the following five groups: inclusion group, non-patient group, intervention group, outcome group and awaiting group. Two reviewers will use Microsoft Excel to encode the included studies and extract data including general information (author list, publication year and journal), characteristics of the included Trials(diagnostic criteria, age range, intervention details), outcome data extraction (numbers of response events and non-response events, dropouts, time points, mean and standard deviation). The risk of bias assessed by the Cochrane risk of bias assessment tool[20]. If there is any missing data, the corresponding authors will be contacted when it is necessary. The studies will be excluded if we can't get access to the data and the reason for exclusion will be reported.

The process will be presented with a PRISMA flow chart (http: //www.prismastatement.org) (figure 2).

Quality assessment

Two reviewers will independently evaluate the methodological quality with the Cochrane Collaboration Risk of Bias Tool[20]. Six domains are included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. And each entry will be categorised into low, high, or unclear risk of bias. Any disagreement between the two reviewers will be resolved through discussion with a third reviewer.

The quality of evidence for the main outcomes will be assessed with the GRADE approach by two reviewers covering study limitations, inconsistency, indirectness, imprecision and publication bias. The quality assessment procedure including following steps: (1) present direct and indirect effect estimates; (2) evaluate the

quality of direct and indirect estimates; (3) present the results of the network meta-analysis and (4) evaluate the quality of the network meta-analysis effect estimates[21].

Network meta analysis

We will use STATA14.0 and WinBUGS1.4.3 to perform the analysis. We will use a random effects model to combine the data. Data on two groups using different technology of identical acupuncture method will be merged according to The Cochrane Handbook for Systematic Reviews of Interventions. Continuous outcomes will be calculated as standardized mean differences (SMDs) and binary outcomes will be calculated as odds ratios(ORs). Both types of effect sizes will be presented with 95% credible intervals (Cr I) and $p < 0.05$ will be regarded as significant. The node splitting method will be used to evaluate the inconsistency of each closed loop[22]. A p-value will be generated to assess the inconsistency of direct and indirect estimates and $p<0.05$ indicates the presence of inconsistency. The bayesian inference will be undertaken using the Markov chain Monte Carlo (MCMC) method. The number of iterations will be set to 50,000, and the first 10,000 iterations for annealing will be set to eliminate the influence of the initial value. Gelman-Rubin Statistic will be used to evaluate the convergence of the simulations.Furthermore, The mean ranks and surface under the cumulative ranking curve (SUCRA) will be presented as percentages an graphs to sequence the probabilities of the optimal intervention. The evidence relationship of included studies will be figured out as a network plot and the result figures and network meta-analysis graphs will be presented.

Sensitivity analysis and subgroup analysis

We will explore the sources of heterogeneity by performing a network meta-regression using a random effects network meta-regression model. If the number of included studies is sufficient, we will conduct a subgroup analysis on region and race. In order to obtain a stable conclusion, we will conduct a sensitivity analysis to eliminate the effect of small sample size trails, studies not reporting blinding, and studies rated as high risk of bias on account of the methodological quality can make big influences of the results.

Publication bias

Publication bias will be evaluated by performing Egger's regression test which can avoid the observation bias of using a funnel plot by indicating a digital result.

Patient and public involvement

No patient and public will be involved.

Discussion

In China, acupuncture therapies in treating acute migraine is diversified and the selection of them is not yet standardized.Hence, clinicians always perform a combination of several methods,which brings a heavy economic burden on patients and lead to a waste of medical resources. In recent years, controlled clinical trials have been increasing but the quality of them was uneven. Network meta-analysis can be used to integrate direct and indirect comparisons[23], which can not only strengthen inferences of efficacy but also rank the efficacy of treatments[24]. In order to generate a reliable evidence, we will perform a rigorous inclusion criteria and the quality will be assessed by GRADE framework.Therefore, we will get a prioritization regimen of the acupuncture treatment for acute migraine. To the best of our knowledge, the present study will be the first network meta-analysis of acupuncture methods for acute migraine. We hope the results will provide a credible evidence supporting the use of acupuncture and be significant for the clinical application of acupuncture methods using as an alternative therapy. We will update this protocol if it must be changed in the future. The date of amendments and the description of changes will be presented as a supplement.

Acknowledgements The authors are grateful to Haoying Zhou for her helpful assistance.

Author Contributions JZ and CW conceived of the study and drafted the protocol.JL1,JL2 and JY revised it. JZ, JL1 and JL2 developed the search strategies and they will run it. JZ and JL1 will select studies and extract data. JZ and JY will analyse the data. All authors have approved the final edition of the protocol**.**

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Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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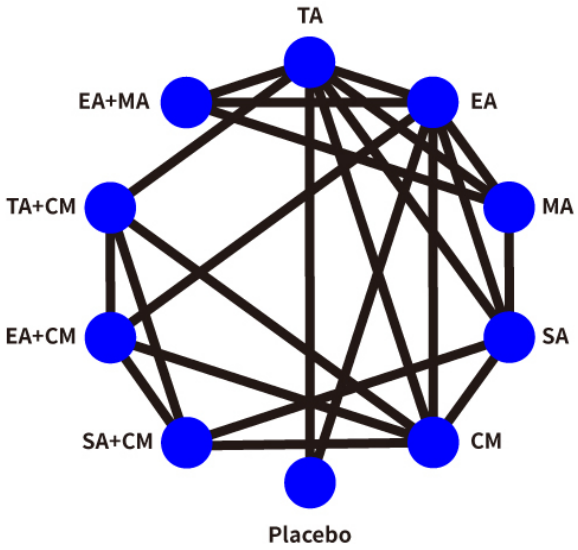
Figure legend

Figure 1 network plot of all possible direct comparisons (TA: traditional manual acupuncture, EA: electroacuppuncture, MA: moxibustion acupuncture, SA: Sham acupuncture, CM: conventional medicine)

Figure 2 PRISMA flow diagram of the study selection process.



network plot of all possible direct comparisons (TA: traditional manual acupuncture, EA: electroacuppuncture, MA: moxibustion acupuncture, SA: Sham acupuncture, CM: conventional medicine)

213x151mm (100 x 100 DPI)

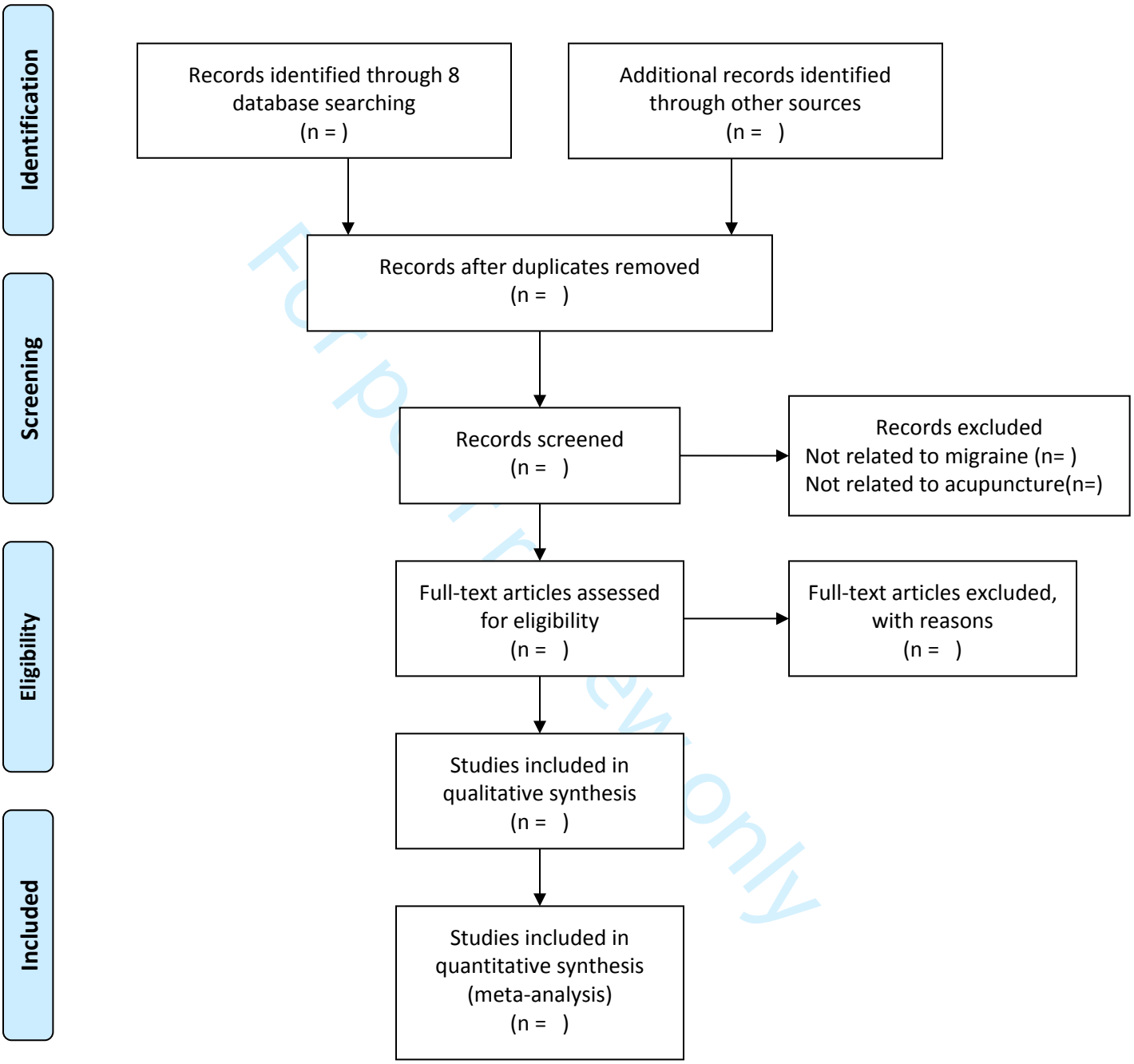


Figure 2 PRISMA flow diagram of the study selection process.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 1
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Page 7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments Page 7
Support:		
Sources	5a	Indicate sources of financial or other support for the review Page 7
Sponsor	5b	Provide name for the review funder and/or sponsor Page 7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 7
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Page 2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 3
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 4-5
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 5

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 5-6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Page 5-6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis Page 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Page 6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) Page 6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Page 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Page 6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Acupuncture methods for acute migraine attack: a Bayesian network meta-analysis protocol

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Abstract

Introduction Migraine is a globally occurring main cause of disability worldwide particularly in young adult and middle-aged women. While drugs are the first line treatment for acute migraine attack, drug overuse not only generates gastrointestinal and cardiovascular disorders but can also induce increased pain and more frequent attacks. Multiple clinical trials and systematic reviews have suggested that acupuncture may be an effective course of treatment for acute migraine attacks but methodologies in academic studies as well as commonly applied practices have been highly varied. In this study protocol we outline a plan to aim to assess and rank the effectiveness of these different acupuncture methods such that we could develop a prioritized acupuncture-based treatment regimen for acute migraine attack.

Objective To compare the efficacy of all acupuncture methods with conventionally-based medicinal methods for the treatment of patients with acute migraine attack.

Methods and analysis Six databases will be searched including MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL),China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP) and Wanfang Database from inception to 31 August 2019. The primary outcomes will be assessed using metrics for pain intensity and duration post-treatment characterized by pain in terms of hours. Bayesian network meta-analyses will be conducted using WinBUGS1.4.3. Finally, we will use the

Grading of Recommendations Assessment, Development and Evaluation System to assess the quality of evidence.

Ethics and dissemination The results will be disseminated through peer-reviewed publication. Any private and confidential patient data will not be contained in the reporting, therefore, there is no ethical considerations associated with this protocol to report.

PROSPERO registration number CRD42019126472

Strengths and limitations of this study:

► This study will be the first ever Bayesian based network meta-analysis for comparison of acupuncture based methods to treat acute migraine.

► The quality of evidence will be assessed by the Grading of Recommendations Assessment, Development and Evaluation System.

► Our research approach will focus upon acupuncture methods, but without discussion of associated acupoint selection and without analysis of the detailed specifics of acupuncture techniques.

►We will only retrieve data from Chinese and English databases which could limit available data or result in language bias.

Key words: Migraine Disorders; Acupuncture; Network Meta-Analysis; systematic review; protocol

Introduction:

Description of the condition

Migraine is a neurological disease characterized by recurrent attacks of unilaterally located headache of a pulsating quality and moderate or severe intensity, aggravation through routine physical activity, and is associated with nausea and/or photophobia and phonophobia[1]. Untreated or unsuccessfully treated attacks can last 4-72 hours and brings a seriously impact patient quality of life. In accordance with the seminal 2016 Global Burden of Neurological Disorders Study[2], migraine is a main global-scaled cause of disability particularly for young adult and middle-aged women. Further, migraine ranked as the second largest contributor of neurological disability-adjusted life-years(DALYs).

Although exact causes and dynamics of migraine remain unclear among groups and individuals, it is now widely accepted that migraine has a strong genetic basis which should be viewed as part of the complex systems making up the brain network and involving multiple cortical, subcortical and brainstem regions[3]. However, despite increasing awareness and clinically based research of migraine, relatively little progress in therapeutics that can effectively control symptoms and which are clearly understood has been made. Triptans, ergotamine derivatives, NSAIDs and opioids are widely considered to be effective in treating acute migraine attack[4]. Nevertheless, the potential and realized side effects from courses of treatment with such drugs should not be underestimated and can be severe. Beyond potentially inducing gastrointestinal and cardiovascular disorders[5][6], pain levels become increasingly worse when patients take painkillers or triptan drugs too frequently and for too long, which can result in abuse of such substances, or the eventual decrease of their effectiveness that may get themselves into a vicious cycle[7]. Side effects of substance abuse drive people to seek nonpharmacologic therapies, thus, developing safe and effective alternative therapies for acute migraine attack is a high priority.

Description of the intervention

Acupuncture is one of the main and most used therapies in Traditional Chinese Medicine(TCM). Acupuncture is accomplished by inserting needles into skin at specific areas of the body (acupoints) or by making insertions along central meridians at certain depths under the skin[8]. Acupuncture produces a sensation of “De qi” simultaneously, which is often described as a sour, numb radiating or distending pain.

The characteristics of sensations can be enhanced by concurrently using electrical stimulation (electroacupuncture), heat (moxibustion acupuncture), or frequent manual stimulation (manual acupuncture)[9]. Electroacupuncture combines needling and electric stimulation. The stimulator connects needles of 2 points, and releases pulses of electric current to generate continuous stimulation when needles are retained in the skin. Moxibustion acupuncture uses applied heating of the needle by burning mugwort on the needle handle after its’ insertion into the body. Fire needling is an acupuncture method which punctures and removes a red-hot needle from a point upon the skin. According to the theory of traditional Chinese acupuncture, fire needling has the functions of warming the meridians and dispelling cold, clearing and activating meridians and collaterals. These methods are what we seek to investigate. The selected acupoints are based on the traditional Chinese acupuncture and are mainly ashi points, local or distal acupoints along meridians, specific acupoints and comprehensively selected acupoints[10].

TCM philosophies focus on maneuvers meant to balance life energy, but the dynamics of the mechanism is difficult to assess from a strictly scientific standpoint study[11]. Biochemical evidence has however shown that acupuncture increases the

activity of the opioidergic system and induces the release of serotonin, dopamine, neurotrophins, and nitric oxide, consequences which may be effective for treating disorders like migraine[12]. Although exact mechanisms are unresolved, acupuncture is a still widely used and accepted approach for migraine treatment. According to a USA-based survey, 9.9 % of patients who underwent treatment for migraine or other headaches used acupuncture to help alleviate symptoms[13]. In recent years, controlled clinical trials on acute or chronic migraine have increased in number and experimental breadth[14-17]. Further, several Cochrane systematic reviews have confirmed the effectiveness and safety of acupuncture[18][19]. However, heretofore few rigorous or no systematic reviews what so ever have assessed acupuncture for treatment of or related to acute migraine and most respective literature has only considered evidence from comparisons of results from acupuncture methods with medicine or sham acupuncture and failed to compare results from all available acupuncture methods. Therefore, determining the best acupuncture methods for relieving pain is intractable. In the present study, we will choose manual acupuncture, electroacupuncture, moxibustion acupuncture and fire needling as the objects based on the theory of TCM.

Objectives

Objectives of this systematic review and network meta-analysis are to: (1) compare and rank all acupuncture methods in terms of efficacy in the treatment of migraine; and (2) produce a credible evidence of the comparison of acupuncture methods and conventional medicine for migraine. We expect that outcomes will provide evidence to better informing the status of the current controversy of acupuncture, and we expect to provide an important summarization of literature based references for helping to inform clinical practices and health policy decision makers.

Methods:

This protocol will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement and the Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis[20,21]. The research has been registered on PROSPERO (CRD42019126472, supplementary file 1 for PRISMA-P checklist).

Eligibility criteria

Types of studies

We will only use data from randomized controlled trials (RCTs) published in English or Chinese without any regional restrictions. The first period of randomised cross-over trials will be included. Literature reviews, animal studies,

retrospective studies, case reports and studies with unavailable data will be excluded.

Types of participants

Participants were adults suffered from "acute migraine" according to the Headache Classification Subcommittee of the International Headache Society[1] definition or any other accepted diagnostic guidelines. Participants with migraines who have had a definite cause identified such as intracranial lesions will be excluded from our analyses. Results will not be analyzed according to gender or nationality will not be limited.

Types of intervention

Our selection of acupuncture methods for analysis will include traditional manual acupuncture (TA), electroacupuncture (EA), moxibustion acupuncture (MA, needle warming through moxibustion), fire needling (FA), a combination of any two of these methods, or combinations of any of these acupuncture methods with conventional based medicines (CM) regardless of acupoint selection or needling techniques. In accordance with outlined standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)[22], rationales related to acupuncture will be limited to traditional Chinese medicine, and neither the period when the research had been conducted nor the duration of the research will be restricted in analyses. Therefore, non-traditional ear acupuncture and wrist-ankle acupuncture will be excluded. In addition, dry needle, laser acupuncture, bee venom acupuncture, acupotomy, as well as any irrelevant treatments such as blood letting therapy, cupping, and herbal medicine will be excluded from our data set and analyses. Figure 1 illustrates the network plot of all possible direct comparisons.

Types of control groups

Different acupuncture methods will form the bases for control group, and will also include both a placebo group as well as a conventional medicine based group. Trials comparing two acupoint selections or acupuncture manipulations will be excluded.

Types of outcome measures

Studies reporting one or more of the following outcomes will be included.

Primary outcomes

A main objective of this review will be the evaluation of analgesic effects of different acupuncture methods for treating acute migraine attack. Hence, primary

desirable outcomes desirable include the pain reduction within 2 hours of treatment and reductions in the duration of pain after treatment.

Levels of pain intensity was measured through headache score rating scales such as a VAS as well as by using a numerical rating scale (NRS) [23] wherein each will be used to assess affects from the time of treatment conclusion through 2 hours post-treatment. Many studies have examined the corresponding relationships with time, thus, for our study we will select the score or other applicable measure at 2 hours time elapsed since treatment, or if this time may be unavailable in the data set, we will choose the closest time available to the 2 hours mark as the temporal measure to be included in this study. We will also measure the duration post-treatment characterized by pain will in terms of hours.

Secondary outcomes

Secondary outcomes will include: 1) the percentage of participants with ≥ 50% pain reduction 2 hours post-treatment; 2) the percentage of participants that were headache-free 2 hours post-treatment[24]; and 3) characterization of adverse events directly related to intervention as reported to assess measures of safety.

Search strategy

We will search the following electronic database: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), and the Wanfang Database. Furthermore, we will search clinical trial registries, academic dissertations, research conference proceedings and grey literature to reduce publication bias in our data. Data from literature reviews and meta-analyses will also be manually searched in case of omissions of data in traditionally styled reporting. Search dates will be from the inception of online databases until 31 August 2019 and languages searched will be limited to either English or Chinese. The retrieval mode used will be a combination of free words and MeSH terms including Migraine Disorders, migraine, acupuncture therapy, acupuncture, electroacupuncture, moxibustion acupuncture and so forth until we feel we have exhausted all possibilities for and relates to all highly applicable search terms. The search strategy for PubMed is shown in table 1.

Table 1	Search strategy used for the PubMed database
No.	Search terms

1	randomized controlled trial [pt]
2	controlled clinical trial [pt]
3	randomized [tiab]
4	placebo [tiab]
5	clinical trials as topic [mesh: noexp]
6	randomly [ab]
7	trial [ti]
8	OR 1-7
9	humans [mh]
10	8 AND 9
11	Migraine Disorders[Mesh]
12	migraine
13	migrain*
14	OR 11-13
15	10 AND 14
16	acupuncture therapy[Mesh]
17	acupuncture treatment
18	pharmacoacupuncture treatment
19	pharmacoacupuncture therapy
20	acupuncture[Mesh]
21	electroacupuncture
22	moxibustion acupuncture
23	warming needle moxibustion
24	fire needling

25	fire needle
26	fire acupuncture
27	OR 16-26
28	15 AND 27

Study selection and data extraction

One reviewer will perform the searches according to designated search strategies and will download relevant citations. NoteExpress3.0 will be used to remove duplicate literature through electronic and manually based steps. Two reviewers will independently screen the study article titles and abstracts and next retrieve the studies most consistent with the eligibility criteria. Any disagreement between reviewers will be resolved through discussion with a third reviewer. All trials will be allocated to the following five groups: inclusion group, non-patient group, intervention group, outcome group and awaiting group. Two reviewers will use Microsoft Excel to encode and extract parameters from applicable studies including general information (author list, publication year, and journal), characteristics of included trials (diagnostic criteria, age range, intervention details), and outcome data (numbers of response events and non-response events, dropouts, time points, mean and standard deviation). The risk of introduced bias will be analyzed by the Cochrane risk of bias assessment tool[25]. If there is any missing data and when necessary, corresponding authors will be contacted and asked to provide relevant details. Some studies will be excluded if we are unable to get access to the data and in these cases reasons for exclusion will be reported in detail.

The entire stepwise process will be presented using a PRISMA flow chart (http://www.prismastatement.org) (figure 2).

Quality assessment

Two reviewers will independently evaluate methodological quality of data using the Cochrane Collaboration Risk of Bias Tool[25]. Six domains will be included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each entry will be categorized into low, high, or unclear risk of bias. Any disagreements between each of the two reviewers will be resolved through

discussions with a third reviewer.

The level of the quality of evidence for main outcomes will be assessed with the GRADE approach performed independently by two reviewers and considering study limitations, inconsistency, indirectness, imprecision and publication bias. Quality assessments procedure will include the following steps: (1) presentation of direct and of indirect effect estimates; (2) evaluation of quality of direct and indirect estimates; (3) presentation of network meta-analysis results; and (4) evaluation of network meta-analysis effect quality estimations[26].

Network meta analysis

We will use STATA14.0 and WinBUGS1.4.3 to perform the Network meta analysis. Data on the two groups will be resultant from using different technology and instead of identical acupuncture methods, we will merge data according to The Cochrane Handbook for Systematic Reviews of Interventions. We will use the I^2 statistic to assess levels of the heterogeneity. Fixed effects models will be used if the I^2 value is $< 50\%$, otherwise, we will use a random effects model to perform the pairwise meta-analysis and to explore main sources of heterogeneity. Continuous outcomes will be calculated as standardized mean differences (SMDs), and binary outcomes will be calculated as odds ratios (ORs). Both types of effect sizes will be presented with 95% confidence intervals (Cr I) and values of $P < 0.05$ will be regarded as statistically significant.

For combining direct and indirect based evidence, we will perform a Bayesian network meta-analysis using a random effects model. The node splitting method will be used to evaluate the inconsistency of direct and indirect estimates in each closed loop according to the resultant P-value[27]. Values of $P > 0.05$ indicate good consistency, otherwise, inconsistencies will be reported ($P < 0.05$). Bayesian Inference will be be analyzed using the Markov chain Monte Carlo (MCMC) method. Iteration number will be set to 50,000, and the first 10,000 iterations for annealing will be set up to eliminate influences of the initial value. The estimation of the Gelman-Rubin Statistic will be used to evaluate convergence of simulations. Furthermore, mean ranks and the area surface under the cumulative ranking curve (SUCRA) will be presented as percentages, and corresponding graphs will be produced to sequence the probabilities of an optimal intervention. Evidence in support of relationships of included studies will be determined by analysis of a network plot and resultant figures and network meta-analysis graphs will be presented.

Assessment of heterogeneity

Examination of clinical and methodological heterogeneity will be focused upon participants' characteristics, interventions and outcomes of the included trials, and upon making comparisons of the goodness of fit of the fixed-effects model and random-effects model. Statistical heterogeneity will be assessed quantitatively using the I^2 statistic. Values of $I^2 < 50\%$ will indicate that heterogeneity is not salient for the cases we seek to explore. Meta-analysis will be performed after removal of studies where main or unacceptable sources of heterogeneity were derived. Furthermore, if the source of heterogeneity can not be explored, we will give a narrative review.

Assessment of transitivity and similarity

In order to produce a credible and valid result, an assessment of transitivity and similarity will be necessary. However, as it is difficult to identify the transitivity and similarity using statistical analysis, they will be assessed based on clinical and methodological characteristics including participant characteristics (age, pain degree), study designs (blind method and risk of bias) and interventions (duration of treatment and needling techniques). All of these research aspects and influential factors will be investigated and reported upon.

Sensitivity analysis and subgroup analysis

We will explore sources of heterogeneity by performing a network meta-regression using a random effects network meta-regression model. If the number of included studies is sufficient, we will conduct an analysis of sub-groups organized according to geographical region and race. In order to obtain a stable conclusion, we will conduct a sensitivity analysis to eliminate effects of trials with small sample size, will eliminate studies not reporting a blind approach to procurement and analysis of data, and will eliminate studies rated as having a high risk of bias based upon accounting of methodological quality. These steps will be crucial to ensure the accuracy and depth of inferences from results.

Publication bias

Publication bias will be evaluated through an Egger's Regression Test from which interpretations will help to avoid observation bias and produce a funnel plot showing indicating a digitally based modeling result.

Additional analyses

With respect to the potential differences of acupoint selection as well as amounts of stimulation between each acupuncturist, we expect that some correlation between observed and inferred levels of the heterogeneity will be likely to objectively exist. On account of its importance in clinical terms, we will conduct a descriptive analysis of acupoint selection, needling techniques, the amount of electrical stimulation, or any other factors that were detailed in included studies that may generate heterogeneity in outcomes of treatment.

Patient and public involvement

No patients and members of the public will be directly involved. Only data already available in the literature and other aforementioned sources will be used for this study.

Discussion

In China, acupuncture therapies for the treatment of acute migraine are diverse, and the appropriate selection of the many subsets and approaches that could be specific to an individual's course of treatment are not yet to be standardized. Hence, clinicians always perform combinations of up to several acupuncture-based methods. The need to explore multiple methodologies to determine what works best increases the burdens of time and financial investment patients may be required to make, as well as leading to increased levels of inefficiency and waste of medical resources. In recent years, controlled clinical trials have been performed in increasing numbers, but the quality of the research has been uneven, and methodologies often limited without considering multiple factors at once. Network meta-analysis can alternatively be used to integrate direct and indirect comparisons across a set of multiple variables[28], which can strengthen inferences of efficacy and help to rank comparative efficacy of differentially composed courses of acupuncture treatments[29]. In order to generate reliable experimentally based evidence on a larger scale than has been done for limited types of single studies, we will perform a rigorous analysis with multiple inclusion criteria factors and quality scores for results that will be assessed by a GRADE based framework.Therefore, we expect that our results will provide a much needed and novel prioritization regime for acupuncture treatment aimed at mitigating or alleviating acute migraine. To the best of our knowledge, the present study will be the first network meta-analysis of acupuncture methods for the treatment of acute

migraine. We hope results will provide credible evidence in support of the beneficial use of acupuncture and be significant enough for an increased and wider acceptance of the positive and measureable clinical applications of acupuncture as an alternative therapy. We will update this protocol if it must be changed in the future. The date of amendments and the description of changes will be presented as a supplement.

Ethics and dissemination

The results will be disseminated through peer-reviewed publication. Any private and confidential patient data will not be contained in the reporting, therefore, there is no ethical considerations associated with this protocol to report.

Acknowledgement The authors are grateful to Haoying Zhou for her helpful assistance.

Author Contributions JZ and CW conceived of the study and drafted the protocol.JL1,JL2 and JY revised it. JZ, JL1 and JL2 developed the search strategies and they will run it. JZ and JL1 will select studies and extract data. JZ and JY will analyse the data. All authors have approved the final edition of the protocol**.**

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Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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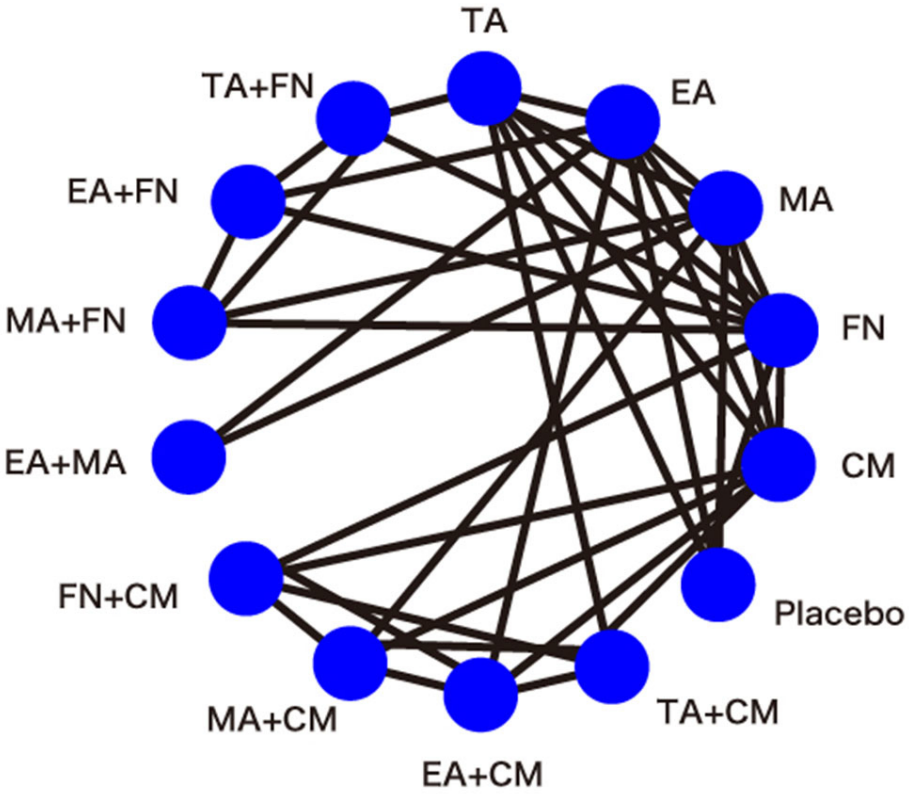
Figure legend

Figure 1 network plot of all possible direct comparisons (TA: traditional manual acupuncture, EA: electroacuppuncture, MA: moxibustion acupuncture, FN: fire needling, CM: conventional medicine)

Figure 2 PRISMA flow diagram of the study selection process.



network plot of all possible direct comparisons (TA: traditional manual acupuncture, EA: electroacuppuncture, MA: moxibustion acupuncture, FN: fire needling, CM: conventional medicine)

375x375mm (72 x 72 DPI)

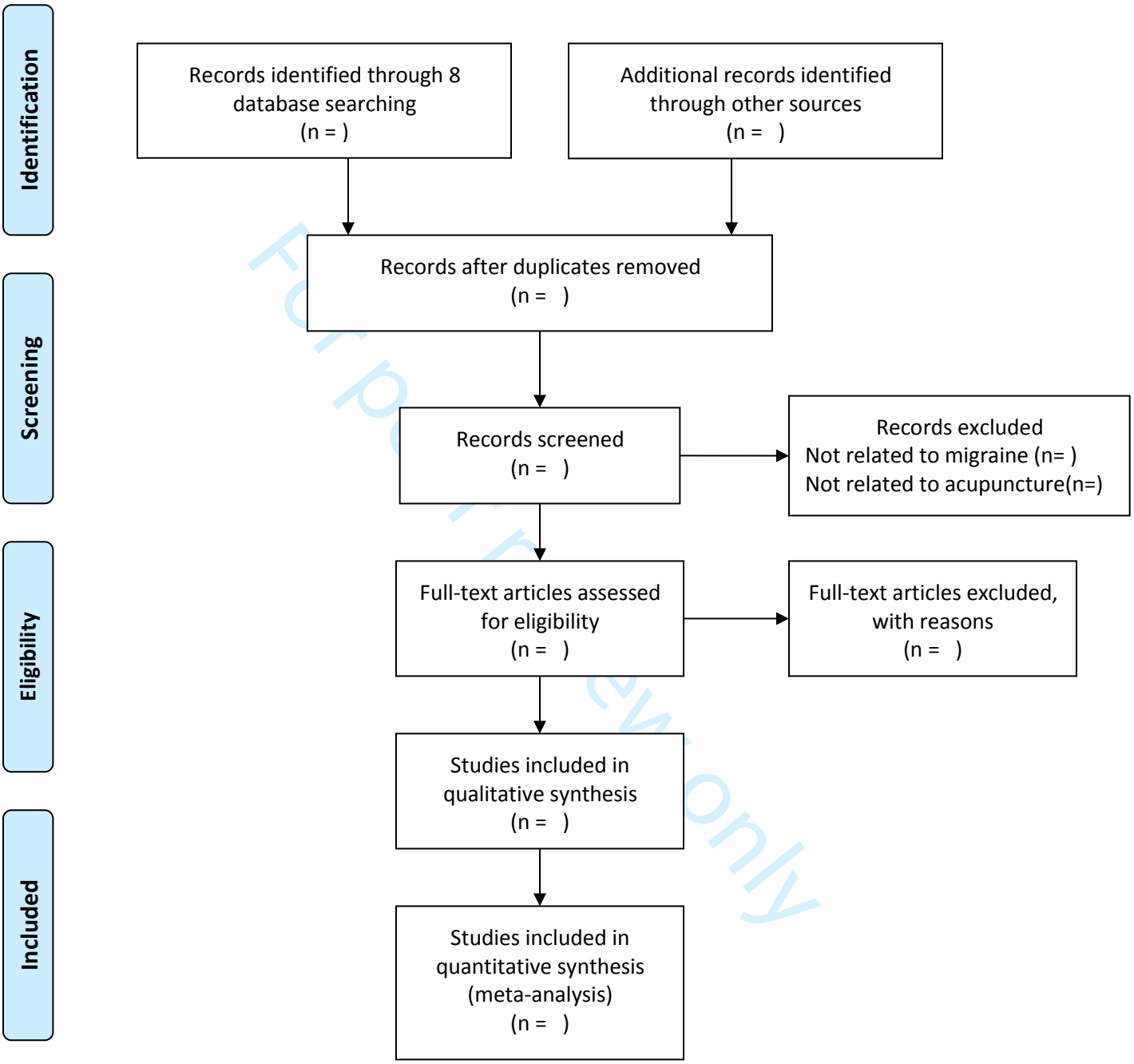


Figure 2 PRISMA flow diagram of the study selection process.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Page 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments Page 12
Support:		
Sources	5a	Indicate sources of financial or other support for the review Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor Page 12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 12
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Page 2-3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 4-6
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 4-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 6-8
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 8

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Page 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 5-6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) Page 9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Page 11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Acupuncture methods for acute migraine attack: a Bayesian network meta-analysis protocol

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Acupuncture methods for acute migraine attack: a Bayesian network meta-analysis protocol

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Abstract

Introduction Migraine is a primary cause of disability worldwide, particularly affecting young adults and middle-aged females. Although multiple clinical trials and systematic reviews have suggested that acupuncture could be effective in treating acute migraine attacks, the methodologies in academic studies and commonly applied practices vary greatly. This study protocol outlines a plan to assess and rank the effectiveness of the different acupuncture methods in order to develop a prioritized acupuncture-based treatment regimen for acute migraine attacks.

Objective To compare the efficacy of different acupuncture methods and conventional medicinal methods in the treatment of acute migraine attacks.

Methods and analysis Six databases will be searched, including MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials,China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database and Wanfang Database from inception to 31 August 2019. The primary outcomes will be assessed using metrics for intensity and duration (in hours) of pain post-treatment. Bayesian network meta-analysis will be conducted using WinBUGS1.4.3. Finally, we will use the Grading of Recommendations Assessment, Development and Evaluation System (GRADE) to assess the quality of evidence.

Ethics and dissemination The results will be disseminated through peer-reviewed publication. Since no private and confidential patient data will be contained in the reporting, there are no ethical considerations associated with this protocol.

PROSPERO registration number CRD42019126472

Strengths and limitations of this study:

► This study will be the first ever Bayesian network meta-analysis comparing acupuncture-based methods in the treatment of acute migraine.

►The quality of evidence will be assessed by the GRADE System.

► Our research approach will focus upon acupuncture methods, but without any discussion about the associated acupoint selection or analysis of the specific details of acupuncture techniques.

►We will only retrieve data from Chinese and English databases which could limit available data or result in language bias.

Key words: Migraine Disorders; Acupuncture; Network Meta-Analysis; systematic review; protocol

Introduction

Description of the condition

Migraine is a neurological disease characterized by recurrent attacks of unilateral headache of a pulsating quality and moderate or severe intensity, aggravated by routine physical activity and associated with nausea and/or photophobia and phonophobia[1]. Untreated or unsuccessfully treated attacks last 4-72 hours and have a serious impact patient quality of life. In accordance with the seminal 2016 Global Burden of Neurological Disorders Study[2], migraine is the main globally-scaled cause of disability, particularly affecting young adults and middle-aged females. Furthermore, migraine has ranked as the second largest contributor of disability-adjusted life-years among neurological disorders.

Although the exact causes and dynamics of migraine among groups and individuals remain unclear, it is now widely accepted that migraine has a strong genetic basis that should be viewed as part of the complex systems forming the brain network and involving multiple cortical, subcortical and brainstem regions[3]. Despite increasing awareness and clinically based research of migraine, relatively limited progress has been made in therapeutics to clearly understand and control symptoms effectively. Triptans, ergotamine derivatives, non-steroidal anti-inflammatory drugs, and opioids are widely considered effective in treating acute migraine attacks[4]. Nevertheless, the potential and reported side effects of these treatment courses should not be underestimated because they can be severe. Besides potentially inducing

gastrointestinal and cardiovascular disorders[5][6], pain levels worsen when patients consume analgesics or triptan drugs too frequently or for too long, resulting in abuse of these substances or eventual reduction in the effectiveness of these drugs resulting in a vicious cycle[7]. Side effects of substance abuse drive patients to seek non-pharmacological therapies. Therefore, developing safe and effective alternative therapies for acute migraine attacks is of utmost priority.

Description of the intervention

Acupuncture is one of the main and commonly used therapies in Traditional Chinese Medicine (TCM). Acupuncture is accomplished by inserting needles into skin at specific areas of the body (acupoints) or by making insertions along central meridians at certain depths under the skin[8]. This produces a sensation of "de qi" simultaneously, which is often described as a sour, numb radiating or distending pain.

The characteristics of sensations can be enhanced by concurrently using electrical stimulation (electroacupuncture [EA]), heat (moxibustion acupuncture [MA]), or frequent manual stimulation (traditional manual acupuncture [TA])[9]. EA combines needling and electric stimulation. The stimulator connects needles at two points and releases pulses of electric current to generate continuous stimulation when the needles are retained in the skin. MA uses applied heating of the needle by burning mugwort on the needle handle after its' insertion into the body. Fire needling (FA) is an acupuncture method that punctures and removes a red-hot needle from a point in the skin. According to the theory of TCM acupuncture, FA has the functions of warming the meridians and dispelling cold, clearing and activating meridians and collaterals. This study aims to investigate these methods. The selected acupoints are based on the TCM acupuncture, and they are mainly ashi points, local or distal acupoints along meridians, specific acupoints and comprehensively selected acupoints[10].

TCM philosophies focus on manoeuvres meant to balance life energy, but the dynamics of the mechanism is difficult to assess from a strict standpoint of scientific study[11]. However, biochemical evidence has shown that acupuncture increases the activity of the opioidergic system and induces the release of serotonin, dopamine, neurotrophins, and nitric oxide, and the consequences could effectively treat disorders like migraine[12]. Although exact mechanisms are unresolved, acupuncture is still a widely used and accepted approach for migraine treatment. According to a USA-based survey, 9.9% of patients who underwent treatment for migraine or other headaches used acupuncture to help alleviate symptoms[13]. In recent years, controlled clinical trials on acute or chronic migraine have increased in number and experimental breadth[14-17]. Furthermore, several Cochrane systematic reviews have confirmed the effectiveness and safety of acupuncture[18][19]. However, heretofore very few or negligible rigorous systematic reviews have assessed the role of

acupuncture in association with the treatment or any other related factors of acute migraine. Most of the literature only considers evidence obtained by comparing acupuncture methods and medicine or sham acupuncture methods and has failed to compare results of all existing acupuncture methods. Therefore, determining the best acupuncture methods for relieving pain is intractable. In this study, we will choose TA, EA, MA and FA as the objects evaluated by the TCM theory.

Objectives

Objectives of this systematic review and network meta-analysis are to: (1) compare and rank all acupuncture methods in terms of efficacy in the treatment of migraine; and (2) produce a credible evidence comparing efficacy of acupuncture methods and conventional-based medicine (CM) for migraine. We expect that the outcomes will provide evidence to clarify the current controversy surrounding acupuncture, and thus provide an important summary of the literature-based references to help clinical practices and health policy decision-makers.

Methods:

This protocol will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement and the Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis[20,21]. The research has been registered on PROSPERO (CRD42019126472, supplementary file 1 for PRISMA-P checklist).

Eligibility criteria

Types of studies

We will only use data from randomized controlled trials published in English or Chinese without any regional restrictions. The first period of randomised cross-over trials will be included. Literature reviews, animal studies, retrospective studies, case reports and studies with unavailable data will be excluded.

Types of participants

Participants will include adults (≥ 18 years old) suffering from acute migraine according to the definition by the Headache Classification Subcommittee of the International Headache Society[1] or any other accepted diagnostic guidelines. Participants with migraines of a definite identified cause such as intracranial lesions, will be excluded from our analyses. Results will not be analyzed according to sex or nationality.

Types of intervention

Our selection of acupuncture methods for analysis will include traditional manual acupuncture (TA), electroacupuncture (EA), moxibustion acupuncture (MA), fire needling (FA), a combination of any two of these methods, or combinations of any of these acupuncture methods with conventional-based medicines (CM), regardless of acupoint selection or needling techniques. In accordance with the outlined standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)[22], rationales related to acupuncture will be limited to TCM, neither the period when the research had been conducted nor the duration of the research will be restricted in the analyses. Therefore, non-traditional ear acupuncture and wrist-ankle acupuncture will be excluded. Moreover, dry needle, laser acupuncture, bee venom acupuncture, acupotomy, as well as any irrelevant treatments, including blood-letting therapy, cupping, and herbal medicine will be excluded from our data set and analyses. Figure 1 illustrates the network plot of all possible direct comparisons.

Types of control groups

Different acupuncture methods will form the basis for the control group, and which will include both a placebo group as well as a CM group. Trials comparing two acupoint selections or acupuncture manipulations will be excluded.

Types of outcome measures

Studies reporting one or more of the following outcomes will be included.

Primary outcomes

A main objective of this review will be the evaluation of the analgesic effects of different acupuncture methods in the treatment of acute migraine attacks. Hence, the primary desirable outcomes include pain reduction within 2 hours of treatment and reductions in the duration of pain post-treatment.

Levels of pain intensity were measured through headache score rating scales such as the visual analogue scale (VAS) and numerical rating scale (NRS) [23] wherein each scale would be used to assess outcomes from the time of treatment conclusion till 2 hours post-treatment. Many studies have examined the corresponding relationships with time; hence, our study will select the score or other applicable measure 2 hours after treatment. If this time is unavailable in the data set, we will choose the closest time available to the 2-hour mark as the temporal measure to be included in this study. We will also measure the duration of pain in hours post-treatment.

Secondary outcomes

Secondary outcomes will include: 1) percentage of participants presenting ≥ 50% pain reduction 2 hours post-treatment; 2) percentage of participants who were headache-free 2 hours post-treatment[24]; and 3) characterization of adverse events directly related to intervention as reported to assess safety measures.

Search strategy

We will search the following electronic database: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), and the Wanfang Database. Furthermore, we will search clinical trial registries, academic dissertations, research conference proceedings and grey literature to reduce publication bias in our data. Additionally, data from literature reviews and meta-analysis will be manually searched in case of omissions of data in traditionally styled reporting. Search dates will be from the inception of the online databases up to 31 August 2019, and the languages searched will be limited to either English or Chinese. The retrieval mode used will be a combination of free words and Medical Subject Headings terms, including "migraine disorders, migraine, acupuncture therapy, acupuncture, electroacupuncture, moxibustion acupuncture, etc." until we feel we have exhausted all possibilities related to all the highly applicable search terms. The search strategy for PubMed is shown in Table 1.

Table 1	Search strategy used for the PubMed database
No.	Search terms
1	randomized controlled trial [pt]
2	controlled clinical trial [pt]
3	randomized [tiab]
4	placebo [tiab]
5	clinical trials as topic [mesh: noexp]
6	randomly [ab]
7	trial [ti]
8	OR 1-7

9	humans [mh]
10	8 AND 9
11	Migraine Disorders[Mesh]
12	migraine
13	migrain*
14	OR 11-13
15	10 AND 14
16	acupuncture therapy[Mesh]
17	acupuncture treatment
18	pharmacoacupuncture treatment
19	pharmacoacupuncture therapy
20	acupuncture[Mesh]
21	electroacupuncture
22	moxibustion acupuncture
23	warming needle moxibustion
24	fire needling
25	fire needle
26	fire acupuncture
27	OR 16-26
28	15 AND 27

Study selection and data extraction

One reviewer will perform the searches according to designated search strategies and download relevant citations. NoteExpress3.0 will be used to remove duplicate literature through electronic and manual based steps. Two reviewers will

independently screen the study article titles and abstracts and then retrieve the studies most consistent with the eligibility criteria. Any disagreement between reviewers will be resolved through discussion with a third reviewer. All trials will be allocated to the following five groups: inclusion group, non-patient group, intervention group, outcome group and awaiting group. Two reviewers will use Microsoft Excel to encode and extract parameters from applicable studies including general information (author list, publication year, and journal), characteristics of included trials (diagnostic criteria, age range, intervention details), and outcome data (numbers of response events and non-response events, dropouts, time points, mean and standard deviation). The risk of introduced bias will be analysed using the Cochrane risk of bias assessment tool[25]. If there is any missing data and when necessary, corresponding authors will be contacted and asked to provide relevant details. Some studies will be excluded if we are unable to get access to the data and the reasons for exclusion will be reported in detail in these cases.

The entire stepwise process will be presented using a PRISMA flow chart (http://www.prismastatement.org) (Figure 2).

Quality assessment

Two reviewers will independently evaluate methodological quality of data using the Cochrane Collaboration Risk of Bias Tool[25]. Six domains will be included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each entry will be categorized into low, high, or unclear risk of bias. Any disagreements between each of the two reviewers will be resolved through discussions with a third reviewer.

The level of the quality of evidence for main outcomes will be assessed with the Grading of Recommendations Assessment, Development, and Evaluation System (GRADE) approach performed independently by two reviewers and considering study limitations, inconsistency, indirectness, imprecision and publication bias[26]. Quality assessments procedure will include the following steps: (1) presenting direct and indirect effect estimates; (2) rating the quality of direct and indirect estimates; (3) presenting the results of the network meta-analysis; and (4) rating the quality of the network meta-analysis effect estimations.

Network meta analysis

We will use STATA14.0 and WinBUGS1.4.3 to perform the network meta

analysis. Data of the two groups will result from the use of different technology and instead of identical acupuncture methods, we will merge data according to the Cochrane Handbook for Systematic Reviews of Interventions. The I^2 statistic will be used to assess levels of the heterogeneity. Fixed effects models will be used if the I^2 value is < 50%, or else a random effects model will be used to perform the pairwise meta-analysis and to explore the main sources of heterogeneity. Continuous outcomes will be calculated as standardized mean differences (SMDs), and binary outcomes will be calculated as odds ratios (ORs). Both types of effect sizes will be presented with 95% confidence intervals (CIs), and values of $P < 0.05$ will be regarded as statistically significant.

For combining direct and indirect based evidence, we will perform a Bayesian network meta-analysis using a random effects model. The node splitting method will be used to evaluate the inconsistency of direct and indirect estimates in each closed loop according to the resultant P-value[27]. Values of $P > 0.05$ indicate good consistency, and all inconsistencies will be reported ($P < 0.05$). Bayesian Inference will be be analyzed using the Markov chain Monte Carlo (MCMC) method. Iteration number will be set to 50,000, and the first 10,000 iterations for annealing will be set up to eliminate influences of the initial value. For indirect comparison, continuous outcomes will be calculated as SMDs, and binary outcomes will be calculated as ORs. Both types of effect sizes will be presented with 95% credible intervals (CrIs). The estimation of the Gelman-Rubin Statistic will be used to evaluate convergence of simulations. Furthermore, mean ranks and the area surface under the cumulative ranking curve (SUCRA) will be presented as percentages, and corresponding graphs will be produced to sequence the probabilities of an optimal intervention. Evidence supporting the relationships of the included studies will be determined by analysis of a network plot, and resultant figures and network meta-analysis graphs will be presented.

Assessment of heterogeneity

Examination of clinical and methodological heterogeneity will focus on participants' characteristics, interventions and outcomes of the included trials, and on comparisons of the goodness of fit of the fixed effects model and random effects model. Statistical heterogeneity will be assessed quantitatively using the I^2 statistic. Values of I^2 <50% will indicate that heterogeneity is not salient for the cases that we explore. Meta-analysis will be performed after removal of studies where main or unacceptable sources of heterogeneity were derived. Furthermore, if the source of heterogeneity can not be explored, a narrative review will be provided.

Assessment of transitivity and similarity

In order to produce a credible and valid result, an assessment of transitivity and similarity will be necessary. However, as it is difficult to identify the transitivity and similarity using statistical analysis, assessment will be based on clinical and methodological characteristics including participant characteristics (age and pain degree), study designs (blind method and risk of bias), and interventions (duration of treatment and needling techniques). All these research aspects and influential factors will be investigated and reported.

Sensitivity analysis and subgroup analysis

We will explore sources of heterogeneity by performing a network meta-regression using a random effects network meta-regression model. If the number of included studies is sufficient, we will conduct an analysis of the sub-groups organized according to geographical region and race. In order to obtain a stable conclusion, we will conduct a sensitivity analysis to eliminate effects of trials with small sample size, eliminate studies not reporting a blind approach to procurement and analysis of data, and eliminate studies rated as high risk of bias based upon accounting of methodological quality. These steps will be crucial to ensure the accuracy and depth of inferences from results.

Publication bias

Publication bias will be evaluated using an Egger's Regression Test which will help avoid observation bias and produce a funnel plot indicating a digitally based modeling result.

Additional analyses

With respect to the potential differences of acupoint selection and amount of stimulation between each acupuncturist, we expect that some correlation between the observed and inferred levels of the heterogeneity will most likely exist objectively. Because of its clinical importance, we will conduct a descriptive analysis of the acupoint selection, needling techniques, amount of electrical stimulation, or any other factors that were detailed in the included studies that may generate heterogeneity in the treatment outcomes.

Patient and public involvement

No patients and members of the public will be directly involved. Only data already existent in the literature and the aforementioned sources will be used for this study.

Discussion

In China, acupuncture therapies to treat acute migraine attacks are diverse, and the appropriate selection of the method and approach specific to an individual's course of treatment has not yet been standardized. Hence, clinicians always perform combinations of several acupuncture-based methods. The need to explore multiple methodologies to determine what works best for patients increases the burdens of time and financial investment on the patients, as well as increase inefficiency and wastage of medical resources. In recent years, several controlled clinical trials have been performed, but the quality of the research has been uneven and methodologies often limited without considering multiple factors together. Network meta-analysis can alternatively be used to integrate direct and indirect comparisons across a set of multiple variables[28], which can strengthen the inferences of efficacy and help to compare efficacies of different acupuncture treatments[29]. In order to generate reliable experimentally based evidence on a larger scale as compared to limited types of single studies, we will perform a rigorous analysis with multiple inclusion criteria and quality scores for results assessed by a GRADE based framework. Therefore, we expect that our results will provide a much needed and novel prioritization regime for acupuncture treatment aimed at mitigating or alleviating acute migraine attacks. To the best of our knowledge, the present study will be the first network meta-analysis of acupuncture methods for the treatment of acute migraine. We hope that our results will provide credible evidence to support the beneficial use of acupuncture and encourage wider acceptance of the positive measureable clinical applications of acupuncture as an alternative therapy for migraine. We will update this protocol required in the future and the date of amendments and description of changes will be presented as a supplement.

Ethics and dissemination

The results will be disseminated through peer-reviewed publication. Since no private and confidential patient data will be contained in the reporting, there are no ethical considerations associated with this protocol.

Acknowledgement The authors are grateful to Haoying Zhou for her helpful assistance.

Author Contributions JZ and CW conceived of the study and drafted the protocol.JL1,JL2 and JY revised it. JZ, JL1 and JL2 developed the search strategies and they will run it. JZ and JL1 will select studies and extract data. JZ and JY will analyse the data. All authors have approved the final edition of the protocol**.**

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Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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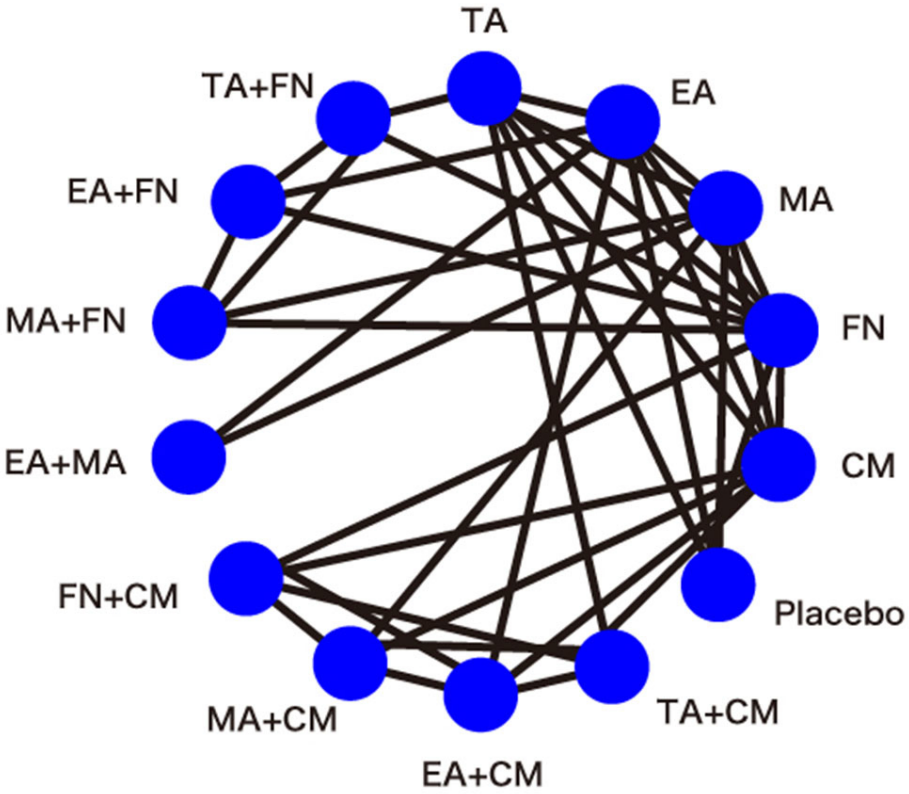
Figure legend

Figure 1 network plot of all possible direct comparisons (TA: traditional manual acupuncture, EA: electroacuppuncture, MA: moxibustion acupuncture, FN: fire needling, CM: conventional medicine)

Figure 2 PRISMA flow diagram of the study selection process.



network plot of all possible direct comparisons (TA: traditional manual acupuncture, EA: electroacuppuncture, MA: moxibustion acupuncture, FN: fire needling, CM: conventional medicine)

375x375mm (72 x 72 DPI)

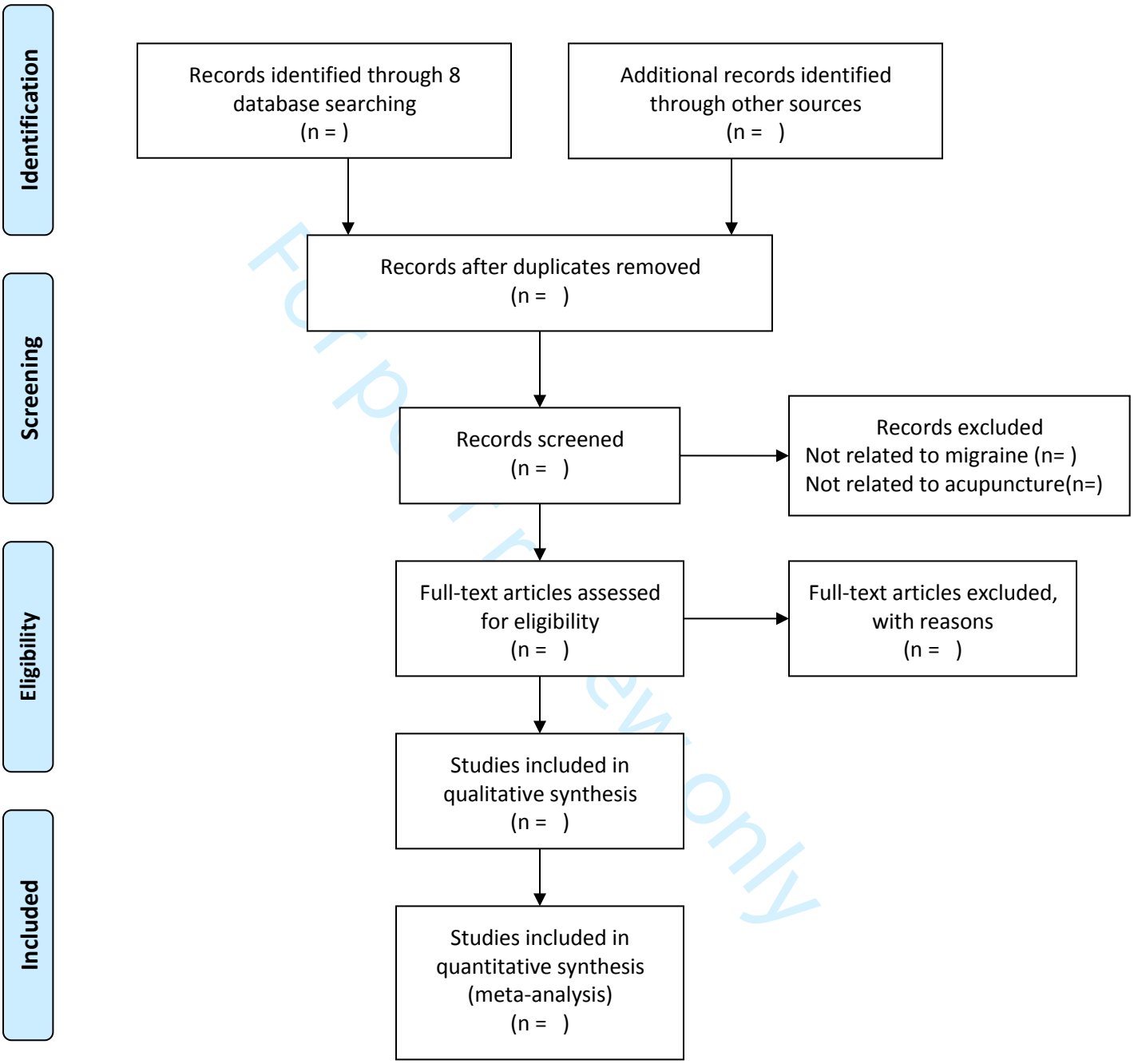


Figure 2 PRISMA flow diagram of the study selection process.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Page 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments Page 11
Support:		
Sources	5a	Indicate sources of financial or other support for the review Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor Page 12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 12
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Page 2-3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 4-6
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 4-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 7-8

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Page 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 5-6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) Page 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Page 9-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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