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Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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ABSTRACT

Introduction

Although the effectiveness of acupuncture for episodic migraine has been confirmed by series of clinical trials and Cochrane systematic reviews, the mechanisms underlying the specific effect of acupuncture for migraine remain controversial. We aim to evaluate the effectiveness and safety of acupuncture for both episodic migraine and chronic migraine by meta-analysis and explore the possible factors influencing the specific effect of acupuncture for migraine by meta-regression.

Methods and analysis

We will search for randomized control trials (RCTs) of acupuncture for migraine in the following eight databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED (via OVID), and four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. We will also search OpenSIGLE (opensigle.inist.fr) for conference abstracts. No language restriction will be applied. The selection of studies, data extraction and coding, and assessment of risk of bias of the include studies will be conducted independently by two reviewers. Standard meta-analysis and, if appropriate, meta-regression will be performed using the R packages Meta and Metafor.

Discussion

The possible findings of this meta-analysis will not only sharpen the understanding of the effectiveness and specific effect of acupuncture for treating migraine, but will also explore how acupuncture treatment can be optimized for migraine in a pragmatic clinical setting.

Ethics and dissemination The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data which will be used do not contain individual patient data, therefore ethical approval is not required.

Trial registration number: PROSPERO CRD42018087270.

Keywords: Acupuncture; migraine; meta-regression; meta-analysis

Strengths and Limitations:

Meta-analysis and the possible meta-regression will be performed by R packages Meta and Metafor, which allow us to detect multiple factors influencing the clinical effect of acupuncture for preventing migraine in the same model.

Searching database for Korean and Japanese will not be used in electronic searches, therefore language bias may exist.

Introduction

Description of the condition

Migraine is one of the most common headache disorders and is characterized by recurrent unilateral, throbbing, moderate-to-severe attacks of headache lasting from 4–72 h, with or without aura [1]. Migraine is commonly associated with symptoms of nausea, vomiting, photophobia, and phonophobia, and is aggravated by physical exertion. According to the 2010 Global Burden of Disease Survey, migraine ranked as the third most predominant disorder, as well as the seventh-highest specific cause of disability worldwide. In the US, an estimated 36 million experience migraine attacks, with approximately 16%–18% of women and 6%–8% of men suffering recurrent migraine attacks during their professional lives [2–3]. Migraine usually can be categorized as episodic migraine (migraine attacks happening fewer than 15 days each month) and chronic migraine (migraine attacks happening more than 15 days per month) [1]. Two large population-based studies documented a strong tendency for episodic migraine to evolve into chronic migraine, often associated with overuse of analgesics [4]. Further, a systematic review focusing on the global prevalence of migraine reported that the prevalence of chronic migraine is 0–5.1%, with estimates typically among 1.4–2.2% [5]. Recently, many studies also demonstrated a correlation between migraine and cardiovascular and cerebrovascular diseases [6-7]. A systematic review investigating migraine and cardiovascular disease found that the risk of ischemic stroke was doubled in people who had migraine with aura [8]. It is well accepted that migraine without aura is associated with ischemic stroke in younger women (age ≤45 years) [9].

Description of the intervention

Effective treatments for migraine are required to reduce the occurrence of migraine attacks and relieve symptoms in order to improve patients' quality of life and decrease related healthcare utilization. Pharmacological agents for migraine are widely used to reduce migraine attack frequency and pain intensity, including propranolol, metoprolol, flunarizine, valproic acid and topiramate [10]. Unlike acute migraine that can often be managed with drugs, chronic migraine is difficult to control due to the frequency of attacks and overuse of drugs among migraine patients [5]. Furthermore, pharmacological treatment for migraine with oral nonsteroidal anti-inflammatory drugs (NSAIDS) and tripans has a modest effect and often leads to several side effects, such as gastrointestinal and cardiovascular disorders [11]. Thus, there is a strong need installing additional long-term effective, low-risk treatments for migraine.

Acupuncture is a procedure whereby fine needles are inserted into and manipulated within the skin at acupoints at certain depths to reduce symptoms and achieve curing of diseases [12]. Acupuncture originate in China and Chinese civilization, and has become one of the most widely used forms of Traditional Chinese Medicine (TCM). The essence of acupuncture lies in the unique meridians and acupoints theory from ancient China, as well as the spirit of holism and personalized treatment. The treatment effect of acupuncture is regarded as balancing the disorder of the human body, to treat diseases by activating accurate meridians and acupoints of the body using diverse needling techniques, according to disease and personal status. Following ancient acupuncture theory, choosing accurate acupoints, applying adequate needling manipulation in sufficient treatment sessions, as well as targeting the corresponding disease and personal status are pivotal aspects for the effect of acupuncture in the clinical setting.

Currently, even without a clear understanding of the mechanism responsible for the effect of acupuncture in Western studies, acupuncture has been used for migraine prophylaxis and chronic pain treatment worldwide. According to a survey in the US, 9.9% of patients who received acupuncture treatment did so in search of relief from

migraine and other headaches [13]. A 2016 Cochrane Review from Germany concluded that acupuncture is safe and effective for episodic migraine prophylaxis compared to prophylactic drug treatment [14].

How the intervention might work

While enhanced calcitonin gene-related peptide (CGRP) and spontaneous cortical spreading depression (CSD) are regarded as causative in triggering migraine [15], the pathophysiology of migraine is attributed to multiple factors, and many of these aspects still remain unclear. Recently, an increasing number of studies has confirmed that acupuncture activates the release of opioid peptides in the central nervous system (CNS), corresponding to long-lasting activation of ascending sensory tracks, thereby relieving an array of pain conditions [16-19]. Furthermore, Zhao LP et al. confirmed in a migraine rat model that electro-acupuncture treatment can depress CGRP expression in the trigeminal ganglion, which plays a key role in inducing migraine attack [20]. Li Z et al. also found that acupuncture restores the impaired descending pain modulatory system (DPMS) in migraine patients by decreasing the resting state functional connectivity (rs-fc) between the periaqueductal gray (PAG) and rostral anterior cingulate cortex/medial prefrontal cortex (rACC/mPFC), which directly correlated with the intensity of pain during the migraine attack [21].

In contrast to the current evidence concerning the mechanism by which acupuncture relieves migraine, evidence of the effectiveness of acupuncture for migraine was provided by a series of Cochrane systematic reviews and a large individual patient meta-analysis [14, 22]. However, the concept of a “placebo effect” and “specific effect” regarding the clinical effect of acupuncture for migraine is still controversial [22]. An updated Cochrane review of acupuncture for episodic migraine concluded that acupuncture is an effective treatment for the prevention of migraine, but on the other hand, the difference in the effect size between acupuncture and sham acupuncture was relatively small [14]. Linde K et al. argued that understanding the specific effect of acupuncture is essential for the acceptance of acupuncture as a legal treatment in Western countries. Therefore, evidence confirming the specific effect of acupuncture is still in high demand for biomedicine [23]. Nevertheless, key

components of the effect of acupuncture remain to be fully uncovered. Accordingly, designing appropriate sham acupuncture as a placebo control is still a difficulty for clinical acupuncture trials. Thus, this debated issue may be an obstacle for both Western scientific researchers and policy makers to accept acupuncture as a valid therapy in pain management.

Why it is important to do this review

To investigate the effect and specificity of acupuncture, a newly update Individual Patient Data Meta-Analysis of acupuncture for chronic pain [24] concluded that true acupuncture has a long-term effect compared with sham acupuncture, but it also pinpointed that characteristics of acupuncture treatment sessions contribute to the effect of acupuncture, in addition to the specific effects of needling. However, this meta-analysis mainly focuses on chronic pain and chronic headache, not specific to migraine. There is still insufficient evidence to elucidate the specific mechanism of the effect of acupuncture for migraine. Furthermore, a recent German Cochrane Review [14] already demonstrated the effectiveness of acupuncture for the prevention of episodic migraine. However, there has been no systematic review of the effect of acupuncture for prevention of chronic migraine. Therefore, three pivotal question arise from the former meta-analysis and clinical studies of acupuncture for migraine: i) Is acupuncture an effective therapy for both episodic migraine and chronic migraine in the clinical setting? ii) Are there any important factors that influence the effect of acupuncture? and iii) Are there any features that alter the specific effect of acupuncture compared with sham acupuncture or other controls in clinical acupuncture treatment for migraine? To address these important questions, we will conduct a meta-analysis of RCTs of acupuncture for migraine.

Objective

This meta-analysis in adults with episodic or chronic migraine aims to assess:

1. the effectiveness and safety of acupuncture compared to sham acupuncture and drug treatment or waiting list controls in the prevention of migraine;
2. features that may contribute to: i) different effect sizes between acupuncture and

controls, ii) the specific effect of acupuncture, iii) non-specific effects of sham acupuncture or other controls, and iv) which factors among all those studied most strongly influence the effect of acupuncture.

Methods

Criteria for considering studies for this review

Types of studies

We will only include RCTs investigating the effect of acupuncture on episodic and chronic migraine in adults [4]. We will only include RCTs (parallel groups as well as cross-over) using well-described randomization and allocation concealment methods.

We will exclude quasi-randomized clinical trials and trials with follow-up less than 8 weeks after randomization. The Cochrane Collaboration's risk of bias tool [25] will be used to assess study quality.

Types of participants

We will include patients of either sex with an age ranging from 18–65 years, who have been diagnosed either with episodic or chronic migraine. Migraine diagnoses must be based on the International Headache Society (ICHD-III beta 2013 and its previous editions ICHD-II 2004; IHS1988) and the Ad Hoc Committee on the Classification of Headache (Ad Hoc 1962) [26-29]. If no specified criteria were documented in the studies, the migraine diagnosis must be based on discriminable and important characteristics of migraine attacks (e.g., recurrent headache, unilateral pain, pulsating quality, moderate or severe intensity, in association with nausea and/or photophobia and phonophobia), as confirmed by patients' doctors or general practitioners. In general, episodic migraine occurs in two to eight episodes but with less than 15 days of migraine attacks per month, whereas chronic migraine patients usually suffer at least 15 days of migraine attacks per month (180 days per year) for at least 3 months [1].

The duration of migraine history must be longer than 1 year in the majority of patients. This criterion will be considered met if:

1) An explicit description of the duration of migraine history longer than 1 year is noted in the inclusion criteria; or

2) The mean duration minus one standard deviation is longer than 1 year as shown in the table of baseline characteristics; or

3) Other information confirms that the criterion was met (e.g., proportions with duration ranges are presented in the studies).

We will include studies in which patients were defined as having 'combination' or 'mixed' migraine only if we can extract the data on participants affected with migraine.

We will exclude trials including patients with secondary headache. Studies including chronic migraine patients with medication-overuse history (according to the International Classification of Headache Disorders, 3rd beta edition (ICHD-IIIß) criteria) will also be excluded.

Types of intervention

Experimental intervention

We define acupuncture (both manual and electrical stimulation) as the experimental intervention. Acupuncture is defined as insertion of specific needles into the skin of the body at selected acupoints (defined as 'meridian acupoints', which belong to 14 meridians in the body according to traditional acupuncture theory) or pain points (defined as 'a-shi points' in the location of pain condition according to traditional acupuncture theory), or extraordinary points (defined as 'extra points', which do not belong to the 14 meridians but have a therapeutic effect in the body according to traditional acupuncture theory) up to definite therapeutic depths. To ensure acupuncture treatment could be clinically effective, the dosage of acupuncture treatment must have at least six treatment sessions, with a duration of at least 20 minutes per session and at least one session per week in the majority of patients. Acupuncturists in the included studies should be confirmed to have a relevant acupuncture qualification or professional affiliation, or years in acupuncture practice. In addition, trials that define acupuncture in combination with other pharmacological treatment or physical treatment as the experimental intervention but mainly

investigate the effectiveness of acupuncture will also be included.

As this meta-analysis will mainly focus on the effectiveness of acupuncture on the basis of traditional acupuncture theory and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [30], we will exclude trials in which:

1) Acupuncture was performed at one of specific body area but not acupoints among the body, such as scalp acupuncture, ear acupuncture, and wrist-ankle acupuncture.

2) Acupoints were stimulated by other techniques without traditional acupuncture needling, including acupressure, laser stimulation, injection acupuncture, dry needling, and trigger point therapy.

Control interventions

We will include three types of control interventions:

1) No treatment or waiting list-control during trial period.

2) Sham acupuncture (intervention resembling verum acupuncture treatment but using superficial needle insertion, needle insertion at non-acupuncture points or at points not indicated for the condition under study, and 'placebo' needles that seem to be inserted into skin but actually are not [31-34], etc). Trials with intervention groups that compared either acupuncture alone with sham intervention alone or acupuncture plus one or more therapies with sham intervention plus the same therapies also will be included.

3) Pharmacological treatment that is given as a control during a comparable time as application of acupuncture treatment.

Because our objective is to evaluate the effectiveness of acupuncture treatment compared to sham acupuncture treatment, no treatment, or western medicine treatment, we will exclude trials with herbal medicine, moxibustion, blooding therapy, and other different forms of acupuncture as control interventions.

Types of outcome measures

To be considered for inclusion, trials must have evaluated at least one of the following primary efficacy outcome measures [35] for at least 4 weeks from the

beginning of acupuncture treatment:

1)Number of migraine attacks per evaluation interval;

2)Number of migraine days per evaluation interval;

Before the review process, a review board consisting of an epidemiologist, acupuncturist, migraine patient, social policymakers, and statistician will be established to determine all the key outcomes, with respect of migraine patients' opinions and values.

We will exclude studies that:

1) Included outcome measurements of any "effectiveness rate";

2)Exclusively used objective or surrogate outcome measures;

3)Evaluated treatment or measurement of acute migraine attack;

4)Had outcome evaluation periods shorter than 4 weeks (after randomization to end of treatment).

According to the guidelines for controlled trials of drugs in migraine published by the IHS [35], the main outcomes will be:

Primary outcome:

Migraine frequency:

We will consider the following outcomes measuring headache frequency:

1）Numbers of migraine attacks per evaluation interval;

2）Number of migraine days per evaluation interval.

Secondary outcomes:

1) Migraine intensity: outcomes recording pain intensity using numerical/verbal scale, such as average headache severity per evaluation interval.

2) Responders rate (patients with ≥50% reduction in headache frequency) per evaluation interval.

3) Medication intake used for migraine per evaluation interval.

4) Adverse events, including the number of patients who dropped out and the number of patients who reported adverse events.

In contrast to previous meta-analysis of acupuncture for prevention of migraine, we define responder rate as a secondary outcome. According to the IHS guideline [35],

the responder rate is comparatively insensitive to the treatment effect and particularly vulnerable to selection bias. The responder rate can be evaluated as an important secondary outcome in placebo-controlled RCTs of migraine.

Outcome measurement may be performed at specific time points; the choice will depend on the time when outcomes are reported in the reviewed studies. Specific decisions will be made by the review board.

The following outcome measures will be presented in the 'Summary of findings' table:

1) Migraine frequency.

2) Migraine intensity.

3) Responder rate.

4) Medication use for migraine attacks.

5) Adverse events.

Search methods for identification of studies

We will conduct our systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and AMED (via OVID) databases as well as four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. No language restriction will be applied. The reference lists of retrieved trials and previous systematic reviews will be searched for citation of potentially eligible trials. We will contact the corresponding author of articles, if any questions about trials arise.

The search strategy for MEDLINE is shown in Table 1.

Table 1 Search strategy to be used in MEDLINE (OVID) database

Number	Search terms
1	Headache Disorders [MeSH]
2	Headache[MeSH]
3	(headache or migraine or cephalgia or cephalalgia or chronic migraine):ti,ab (Word variations have been searched)
4	1 or 2 or 3
5	Acupuncture Therapy [MeSH]
6	(acupuncture or electroacupuncture or electro-acupuncture) :ti,ab
7	5 or 6
8	randomised :ti, ab.
9	randomized :ti,ab.
10	randomly :ti,ab.
11	placebo :ti,ab
12	clinical trials [MeSH]
13	trial ti,ab.
14	randomized controlled trial [MeSH]:ti,ab.
15	randomised controlled trial [MeSH]:ti,ab.
16	controlled clinical trial :ti,ab
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	humans
19	17 and 18
20	4 and 7 and 19

Searching other resources

We will search the US National Institutes of Health Ongoing Trials Register (http://www.clinical trials.gov), the WHO International Clinical Trials Registry Platform (http://www.who.int/trialsearch), and the metaRegister of Controlled Trials (http://www.controlledtrials.com) for any relevant ongoing or unpublished trials. OpenSIGLE (opensigle.inist.fr) will be searched for conference abstracts. We will also search Google Scholar (scholar.google.com/advanced scholar search?hl=en&lr=) using the search string "acupuncture AND (headache OR migraine OR chronic migraine)" for potential relevant trials from inception to December 31, 2017.

Data collection and analysis

Selection of studies

Two independent reviewers will examine titles and abstracts of the identified studies and will exclude irrelevant trials. When the first selection is made, full articles will be obtained and checked again in more detail. Following this assessment, a second selection will be performed. The criteria for both selections will be extracted and documented. Possible conflicts will be resolved by discussion, which will also include a third reviewer. Selection process will be presented in the PRISMA flow diagram(Figure.1)

Data extraction and coding

Two independent reviewers will extract data from the selected studies using pilot-tested data forms. They include the following study information: author, year of publication, study populations (European ancestry or not), study design, numbers of patients randomized and treated, number of patients analyzed, baseline analysis, random sequence generation, allocation concealment method, blinding method, imputation method, withdrawals of data, interventions, controls, and primary and secondary outcomes at all reported time points. For investigating the characteristics of acupuncture effect, we will extract data on age, sex, populations, headache classifications, number and duration of treatment sessions, features of acupuncture treatment (such as type of acupuncture, needle depths, selection of points, achievement of de-chi, manipulation between acupuncture treatment or not), features of control interventions (sham methods, drug use, or standard treatment details), patients' expectations, and experience of acupuncturists in accordance with Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [30].

We also will document to each outcome of interest the percentage of missing values reported in the study.

For the purpose of analyzing the influence of characteristics of acupuncture on its effect size, a coding sheet will be developed to transform all the described data into categorical data. A pilot testing on this coding sheet will be performed on a separate subset of studies. A coding book will be subsequently established to guide the coding

process when the code sheet is completed. Two independent reviewers and statisticians will check the coding sheet when coding process has been finished [36].

Assessing risk of bias in included studies

Two reviewers will independently assess the risk of bias for each included RCTs using the Cochrane Collaboration's risk of bias tool [25]. The critical assessment for the risk of bias will be evaluated in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. This assessment will be achieved by assigning a judgement of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias. Any disagreement will be resolved by discussion or consensus with a third reviewer. The graphical presentation of assessment of risk of bias will be generated by RevMan V.5.3.5.

Measures of treatment effect

To address the clinical effect difference between the intervention and control groups, headache frequency at the completion of treatment and at the end of follow-up will be used as a primary outcome. Pain intensity, responder rate and mediation intake at the completion of treatment and at the end of follow-up also will be extracted as secondary outcomes. For these continuous outcomes, the mean difference (MD) and standard deviations (SDs) will be extracted and calculated as an effect estimate. Negative values will indicate better outcomes in the acupuncture group.

If the MD or SDs were not reported and not available after contacting the authors, we will use the data that is available, such as the median or P values and confidence intervals, and try to re-calculate MD and SD values from the information recorded in the study.

The safety or adverse outcome will be the number of participants who dropped out due to adverse effects and the number of participants who reported at least one adverse event or effect. For these dichotomous outcomes, the odds ratio (OR) will be calculated as the effect estimate. An odds ratio greater than 1 will indicate more events (e.g., dropouts) in the acupuncture group.

For the time window analysis, we will extract outcomes with all the time points

using pilot-tested data forms. Subsequently, we will document the quantitative outcomes at the end of treatment together with the length of the treatment period. In a meta-regression, we will adjust treatment effects for time. Using the R package metafor will allow us to give for each outcome a meta-analytic result at different treatment periods. Standard meta-analyses, especially for subgroups, will be performed using the R-package meta [37-38].

Unit of analysis issues

The unit of analysis will be based on aggregated outcome data due to the lack of individual patient data.

Dealing with missing data

We will perform a sensitivity analysis to elucidate the amount of missing data on the effect estimates. This can be performed by a meta-regression adjusting for the amount of missing data.

Assessment of heterogeneity

We will evaluate heterogeneity of included studies with I^2 statistic and the tau^2 test. A cutoff point of at least 50% in I^2 statistic will be considered as substantial heterogeneity.

Our second aim is to investigate which clinical setting and which acupuncture features do influence the size and the heterogeneity of the intervention. First, we will define characteristics that may modify the intervention effect according to experienced acupuncturists and STRICTA [30]. Second, we will examine the correlation between these covariates to exclude possible masking and to establish a core-set of covariates. A random-effect meta-regression analysis will be conducted using **metafor** [37] to elucidate the impact of core set covariates on treatment effects.

Before the meta-analysis can be conducted, the relevant results from each study must be quantified in such a way that the resulting values can be further aggregated and compared. Depending on different aspects (goals of the meta-analysis, the design and types of studies included, and the information provided therein), we will calculate the effect size of interest using the **escalc** function.

Subsequently, random/mix-effects of the meta-regression model will be fitted by **rma()** function [37]. The r**estricted maximum-likelihood estimator,** which is an

approximately unbiased and efficient estimator, will be used to address the amount of residual heterogeneity tau^2. The pre-defined covariates will be first fitted independently to examine the possible independent factors contributing to variation in the intervention effect. Subsequently, interaction between covariates can be added and detected in the model using the **mods** argument. For the limit of included studies, we will put covariates ≤3 into the same model for each model. For the result interpretation, the **estimate** represents the average effect estimates of covariates, and a P value ≤0.05 represents a significant difference that indicates the corresponding covariate plays an important role for the intervention effect and heterogeneity. In addition, the amount of heterogeneity in the effect estimate will be estimated by **tau^2**. The $\mathbf{I^2}$ statistic estimates (in percent) how much of the total variability in the effect size estimate (which is composed of heterogeneity and sampling variability) can be attributed to heterogeneity among the true effects.

Assessment of reporting biases

Reporting bias will be explored using funnel plot and Egger's test, if there are at least 10 trials included in meta-analysis.

Data synthesis

The synthesis will be done by a forest plot for meta-regression. This plot does not contain a summary measure given by a prism below the single studies, but by a prism which is shown for each single study and which shows the aggregated effect for the type of study which is represented by the specific study (depending on the covariates of the meta-regression). If the heterogeneity test indicates there is no substantial heterogeneity between studies, the Mantel-Haenszel method implemented by the **rma.mh()** function will be fitted for calculating pooled estimates, 95% confidence intervals, and combined P values. If substantial heterogeneity is indicated by $I^2 \geq 50\%$, the random effect model will be performed by the DerSimonian and Laird method (DerSimonian 1986) and the **rma** function. The significance of the P value represents the strength of evidence against the null hypothesis of no intervention effect.

Subgroup analysis

Subgroup analysis will be performed according to the primary and secondary

objectives. To detect possible heterogeneity of the results, subgroup analysis will be conducted for both the primary outcome and secondary outcomes, at the end of the treatment session and the end of the follow-up period. We will investigate the effects for four subgroup analyses:

1) episodic migraine VS chronic migraine
2) acupuncture VS different type of sham acupuncture and controls
3) Western studies VS Chinese studies
4) early time-point of outcomes VS later time-point of outcomes

In addition, if we detect any important and significant covariates contributing to the variation of the intervention effect by meta-regression, subgroup analyses will also be conducted according to these covariates.

Sensitivity analysis

To confirm the robustness of our findings, a sensitivity analysis will be conducted based on the different levels of bias of the included studies. To evaluate the internal validity of studies or treatment adequacy, we will subsequently remove studies of 'high risk' of bias, studies of 'unclear risk' of bias, and studies of 'low risk' of bias using the **metafor** package and **leave1out()** function.

Summary of evidence

We will summarize the quality of evidence using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) [39] and present 'Summary of findings' tables. The 'Summary of findings' tables will be generated by the GRADE working group software (GRADEpro or GRADEpro GDT [www.gradepro.org]). The content of the 'Summary of findings' tables (main outcomes that are important to patients and decision makers) will be determined by the review group described above. Where possible, both relative and absolute measures of effect will be provided. To assess the quality of evidence, the GRADE approach evaluates the quality of evidence as 'high', 'moderate', 'low', or 'very low' by outcome. Evidence can be downgraded in category by concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias, and also can be upgraded by a large effect size, plausible confounding that could change the effect size, and

dose-response relation. Reviewers will downgrade or upgrade the evidence according to the GRADE guideline in the Cochrane handbook, Chapter 11 [25] and also take into account the differences in anticipated effects in the group of primary interest. The total quality of evidence will decided by not only the reviewers but also based on the opinion of patients, decision makers, and acupuncturists. The whole summarization of the evidence process will be succinct and transparent.

Discussion

This meta-analysis will not only evaluate evidence from published RCTs for the effectiveness of acupuncture in treating both episodic migraine and chronic migraine, but also will detect possible characteristics that influence the main effect and the specific effect of acupuncture for migraine. This will be achieved by using meta-regression. We hope that using meta-regression techniques in this meta-analysis will not only provide a deeper understanding of the effect of acupuncture in patients with migraine, but also create evidence for factors that modify the effect, which will support the optimization of acupuncture treatment for migraine in the pragmatic clinical setting. If this protocol must be amended, we will present the date of each amendment with a description of the change and the corresponding rationale.

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Author Contributions

UM is the guarantor. ZG, UM, CG and ZX contributed to the conception of the study. The manuscript presenting the protocol was drafted by ZG and revised by UM. The search strategy was developed by all authors and will be run by ZG and LQ, who will also independently screen the potential studies, extract data from included studies, assess the risk of bias, and finish the data synthesis. CH will arbitrate in cases of disagreement and ensure no errors occur during the study. All authors have approved the publication of the protocol.

Competing interests

None declared

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Data sharing statement: Technical appendix, statistical code and data set are available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the data set.

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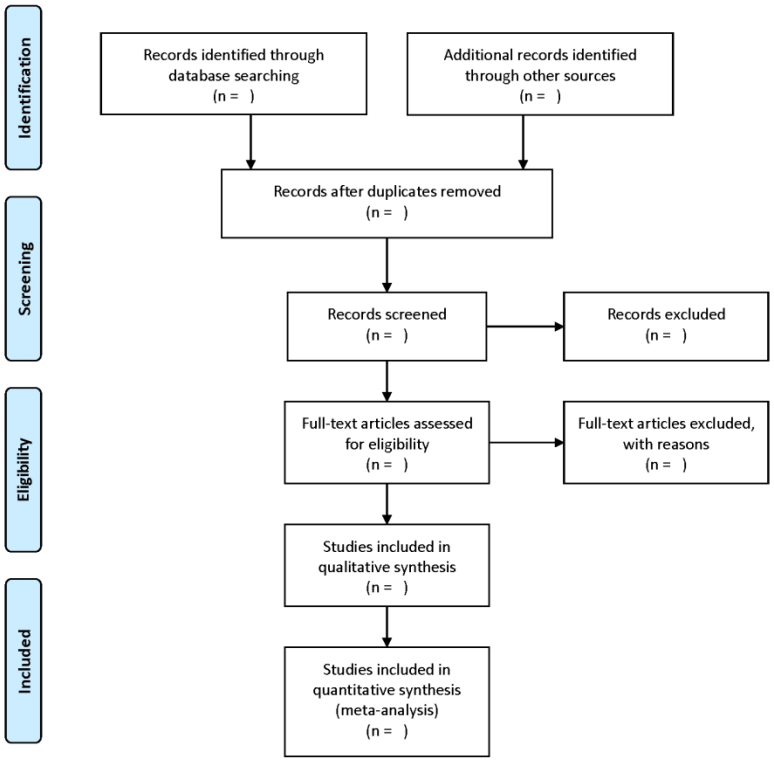

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		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	18
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19
	#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	18

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	19
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	19
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7-10
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	11
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	12
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13
Study records - 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)	13
Study records - 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	13
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	13

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	14
	#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 I2, Kendall's τ)	14-15
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16-17
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17

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Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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ABSTRACT

Introduction

Although the effectiveness of acupuncture for episodic migraine has been confirmed by multiple clinical trials and Cochrane systematic reviews, the mechanisms underlying the specific effect of acupuncture for migraine remain controversial. We aim to evaluate the effectiveness and safety of acupuncture for both episodic migraine and chronic migraine by meta-analysis and explore the possible factors influencing the specific effect of acupuncture for migraine by meta-regression.

Methods and analysis

We will search for randomized control trials (RCTs) of acupuncture for migraine in the following eight databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED (via OVID), and four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. We will also search OpenSIGLE (opensigle.inist.fr) for conference abstracts. No language restriction will be applied. The selection of studies, data extraction and coding, and assessment of risk of bias of the included studies will be conducted independently by two reviewers. Standard meta-analysis and, if appropriate, meta-regression will be performed using the R packages Meta and Metafor.

Ethics and dissemination: The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data that will be used will not contain individual patient data; therefore, ethical approval is not required.

Trial registration number: PROSPERO CRD42018087270.

Keywords: Acupuncture; Migraine; Meta-regression; Meta-analysis

Strengths and Limitations:

1. This meta-analysis will not only evaluate the effectiveness of acupuncture in treating both episodic migraine and chronic migraine but also will detect possible characteristics that influence the main effect and the specific effect of acupuncture for migraine.
2. Equipped with advanced machine learning techniques and R packages Meta and Metafor, this meta-analysis could uniquely explore the interaction and combinatory effects of different clinical factors that may affect the main effect and specific effect of acupuncture for migraine.
3. The results of this meta-analysis may reveal pivotal factors that impact the clinical effect of acupuncture, and thus, will support the optimization of acupuncture treatment for migraine in the pragmatic clinical setting.
4. Electronic databases for Korean and Japanese studies will not be searched; therefore, language bias may exist.

Introduction

Description of the condition

Migraine is one of the most common headache disorders and is characterized by recurrent unilateral, throbbing, moderate-to-severe attacks of headache lasting from 4–72 h, with or without aura [1]. Migraine is commonly associated with symptoms of nausea, vomiting, photophobia, and phonophobia and is aggravated by physical exertion. According to the 2010 Global Burden of Disease Survey, migraine ranked as the third most predominant disorder, as well as the seventh highest specific cause of disability worldwide. In the US, an estimated 36 million individuals experience migraine attacks, with approximately 16%–18% of women and 6%–8% of men suffering recurrent migraine attacks during their professional lives [2–3]. Migraine usually can be categorized as episodic migraine (migraine attacks happening fewer than 15 days each month) and chronic migraine (migraine attacks happening more than 15 days per month) [1]. Two large population-based studies documented a strong tendency for episodic migraine to evolve into chronic migraine, often associated with

overuse of analgesics [4]. Further, a systematic review focusing on the global prevalence of migraine reported that the prevalence of chronic migraine is 0–5.1%, with estimates typically among 1.4–2.2% [5]. Recently, many studies also demonstrated a correlation between migraine and cardiovascular and cerebrovascular diseases [6-7]. A systematic review investigating migraine and cardiovascular disease found that the risk of ischemic stroke was doubled in people who had migraine with aura [8]. It is well accepted that migraine without aura is associated with ischemic stroke in younger women (age ≤45 years) [9].

Description of the intervention

Effective treatments for migraine are required to reduce the occurrence of migraine attacks and relieve symptoms in order to improve patients' quality of life and decrease related healthcare utilization. Pharmacological agents for migraine are widely used to reduce migraine attack frequency and pain intensity, including propranolol, metoprolol, flunarizine, valproic acid, and topiramate [10]. Unlike acute migraine that can often be managed with drugs, chronic migraine is difficult to control due to the frequency of attacks and overuse of drugs among migraine patients [5]. Furthermore, pharmacological treatment for migraine with oral nonsteroidal anti-inflammatory drugs (NSAIDS) and tripans has a modest effect and often leads to several side effects, such as gastrointestinal and cardiovascular disorders [11]. Thus, there is a strong need for the development and implementation of additional long-term effective, low-risk treatments for migraine.

Acupuncture is a procedure whereby fine needles are inserted into and manipulated within the skin at acupoints at certain depths to reduce symptoms and achieve curing of diseases [12]. Acupuncture originated in China within the Chinese civilization and has become one of the most widely used forms of Traditional Chinese Medicine (TCM). The treatment effect of acupuncture is regarded as balancing the disorder within the human body in order to treat diseases by activating accurate meridians and acupoints of the body using diverse needling techniques, according to disease and personal status. Currently, even without a clear understanding of the

mechanism responsible for the effect of acupuncture in Western studies, acupuncture has been widely used for migraine prophylaxis and chronic pain treatment worldwide. According to a survey in the US, 9.9% of patients who received acupuncture treatment did so in search of relief from migraine and other headaches [13]. A 2016 Cochrane Review from Germany concluded that acupuncture is safe and effective for episodic migraine prophylaxis compared to prophylactic drug treatment [14].

How the intervention might work

While enhanced calcitonin gene-related peptide (CGRP) and spontaneous cortical spreading depression (CSD) are regarded as causative in triggering migraine [15], the pathophysiology of migraine is attributed to multiple factors, and many of these aspects remain unclear. Recently, an increasing number of studies has confirmed that acupuncture activates the release of opioid peptides in the central nervous system (CNS), corresponding to long-lasting activation of ascending sensory tracks, thereby relieving an array of pain conditions [16-19]. Furthermore, Zhao et al. confirmed in a migraine rat model that electro-acupuncture treatment can depress CGRP expression in the trigeminal ganglion, which plays a key role in inducing migraine attack [20]. Li et al. also found that acupuncture restores the impaired descending pain modulatory system (DPMS) in migraine patients by decreasing the resting state functional connectivity (rs-fc) between the periaqueductal gray (PAG) and rostral anterior cingulate cortex/medial prefrontal cortex (rACC/mPFC), which directly correlated with the intensity of pain during the migraine attack [21].

In contrast to the conflicting evidence concerning the mechanism by which acupuncture relieves migraine, evidence of the effectiveness of acupuncture for migraine was provided by a series of Cochrane systematic reviews and a large individual patient meta-analysis [14, 22]. However, the concept of a “placebo effect” and “specific effect” regarding the clinical effect of acupuncture for migraine is still controversial [22]. An updated Cochrane review of acupuncture for episodic migraine concluded that acupuncture is an effective treatment for the prevention of migraine, but on the other hand, the difference in the effect size between acupuncture and sham

acupuncture was relatively small [14]. Linde et al. argued that understanding the specific effect of acupuncture is essential for the acceptance of acupuncture as a legitimate treatment in Western countries. Therefore, evidence confirming the specific effect of acupuncture is still in high demand for biomedicine [23]. Nevertheless, key components of the effect of acupuncture remain to be fully uncovered. Accordingly, designing appropriate sham acupuncture as a placebo control is still a difficulty for clinical acupuncture trials. Thus, this debated issue may be an obstacle for the acceptance of acupuncture as a valid therapy in pain management by both Western scientific researchers and policy makers.

Why is this review important?

To investigate the effect and specificity of acupuncture, a newly updated Individual Patient Data Meta-Analysis of acupuncture for chronic pain [24] concluded that true acupuncture has a long-term effect compared with sham acupuncture, but it also pinpointed that characteristics of acupuncture treatment sessions contribute to the effect of acupuncture, in addition to the specific effects of needling. However, this meta-analysis mainly focused on chronic pain and chronic headache and was not specific to migraine. There is still insufficient evidence to elucidate the specific mechanism of the effect of acupuncture for migraine. Furthermore, a recent German Cochrane Review [14] demonstrated the effectiveness of acupuncture for the prevention of episodic migraine. However, there has been no systematic review of the effect of acupuncture for the prevention of chronic migraine. Therefore, three pivotal questions arise from the former meta-analysis and clinical studies of acupuncture for migraine: i) is acupuncture an effective therapy for both episodic migraine and chronic migraine in the clinical setting? ii) are there any important factors that influence the effect of acupuncture? and iii) are there any features that alter the specific effect of acupuncture compared with sham acupuncture or other controls in clinical acupuncture treatment for migraine? To address these important questions, we will conduct a meta-analysis of RCTs of acupuncture for migraine.

Objective

This meta-analysis in adults with episodic or chronic migraine aims to assess:

1. the effectiveness and safety of acupuncture compared to sham acupuncture and drug treatment or waiting list controls in the prevention of migraine;

2. features that may contribute to: i) different effect sizes between acupuncture and controls, ii) the specific effect of acupuncture, iii) non-specific effects of sham acupuncture or other controls, and iv) which factors among all those studied most strongly influence the effect of acupuncture.

Methods

Criteria for considering studies for this review

Types of studies

We will only include RCTs investigating the effect of acupuncture on episodic and chronic migraine in adults [4]. We will only include RCTs (parallel groups as well as cross-over) using well-described randomization and allocation concealment methods.

We will exclude quasi-randomized clinical trials and trials with follow-up less than 8 weeks after randomization.

Types of participants

We will include patients of either sex with an age ranging from 18–65 years who have been diagnosed either with episodic or chronic migraine. Migraine diagnoses must be based on the International Headache Society (ICHD-III beta 2013 and its previous editions ICHD-II 2004; IHS1988) and the Ad Hoc Committee on the Classification of Headache (Ad Hoc 1962) [25-28]. If no specified criteria were documented in the studies, the migraine diagnosis must be based on discriminable and important characteristics of migraine attacks (e.g., recurrent headache, unilateral pain, pulsating quality, moderate or severe intensity, in association with nausea and/or photophobia and phonophobia), as confirmed by patients' doctors or general practitioners. In general, episodic migraine occurs in two to eight episodes but with migraine attacks on less than 15 days per month, whereas chronic migraine patients

usually suffer migraine attacks on at least 15 days per month (180 days per year) for at least 3 months [1].

The duration of migraine history must be longer than 1 year in the majority of patients. This criterion will be considered met if:

1) An explicit description of the duration of migraine history longer than 1 year is noted in the inclusion criteria;

2) The mean duration minus one standard deviation is longer than 1 year as shown in the table of baseline characteristics; or

3) Other information confirms that the criterion was met (e.g., proportions with duration ranges are presented in the studies).

We will include studies in which patients were defined as having 'combination' or 'mixed' migraine only if we can extract the data on participants affected with migraine.

We will exclude trials including patients with secondary headache. Studies including chronic migraine patients with medication-overuse history (according to the International Classification of Headache Disorders, 3rd beta edition (ICHD-IIIß) criteria) will also be excluded.

Types of intervention

Experimental intervention

We define acupuncture (both manual and electrical stimulation) as the experimental intervention. Acupuncture is defined as insertion of specific needles into the skin of the body at selected acupoints (defined as 'meridian acupoints', which belong to 14 meridians in the body according to traditional acupuncture theory), pain points (defined as 'a-shi points' in the location of pain condition according to traditional acupuncture theory), or extraordinary points (defined as 'extra points', which do not belong to the 14 meridians but have a therapeutic effect in the body according to traditional acupuncture theory) up to definite therapeutic depths. In accordance with a previous Cochrane systematic review of acupuncture for migraine [14], the dosage of acupuncture treatment must be at least six treatment sessions, with a duration of at least 20 minutes per session and at least one session per week in the

majority of patients. Also, for the purpose of ensuring the clinical effectiveness of acupuncture treatment, the acupuncturists who administered treatment in the included studies should be confirmed to have a relevant acupuncture qualification or professional affiliation, or a certain number of years in acupuncture practice. In addition, trials that define acupuncture in combination with other pharmacological treatment or physical treatment as the experimental intervention but mainly investigate the effectiveness of acupuncture will be included.

As this meta-analysis will mainly focus on the effectiveness of acupuncture on the basis of traditional acupuncture theory and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [29], we will exclude trials in which:

1) Acupuncture was performed at one specific body area but not at acupoints of the body, such as scalp acupuncture, ear acupuncture, and wrist-ankle acupuncture.

2) Acupoints were stimulated by other techniques without traditional acupuncture needling, including acupressure, laser stimulation, injection acupuncture, dry needling, and trigger point therapy.

Control interventions

We will include three types of control interventions:

1) No treatment or waiting list-control during trial period.

2) Sham acupuncture (intervention resembling verum acupuncture treatment but using superficial needle insertion, needle insertion at non-acupuncture points or at points not indicated for the condition under study, and 'placebo' needles that seem to be inserted into skin but actually are not [30-33], etc). Trials with intervention groups that compared either acupuncture alone with sham intervention alone or acupuncture plus one or more therapies with sham intervention plus the same therapies also will be included.

3) Pharmacological treatment that is given as a control during a comparable time as application of acupuncture treatment.

Because our objective is to evaluate the effectiveness of acupuncture treatment compared to sham acupuncture treatment, no treatment, or western medicine

treatment, we will exclude trials with herbal medicine, moxibustion, bloodletting, and other different forms of acupuncture as control interventions.

Types of outcome measures

To be considered for inclusion, trials must have evaluated at least one of the following primary efficacy outcome measures [34] for at least 4 weeks from the beginning of acupuncture treatment:

1) Number of migraine attacks per evaluation interval;

2) Number of migraine days per evaluation interval;

Before the review process, a review board consisting of an epidemiologist, acupuncturist, migraine patient, social policymakers, and statistician will be established to determine all the key outcomes, with respect of migraine patients' opinions and values.

We will exclude studies that:

1) Included outcome measurements of any "effectiveness rate";

2) Exclusively used objective or surrogate outcome measures;

3) Evaluated treatment or measurement of acute migraine attack;

4) Had outcome evaluation periods shorter than 4 weeks (after randomization to end of treatment).

According to the guidelines for controlled trials of drugs in migraine published by the IHS [34], the main outcomes will be:

Primary outcome:

Migraine frequency:

We will consider the following outcomes measuring headache frequency:

1） Numbers of migraine attacks per evaluation interval;

2）Number of migraine days per evaluation interval.

Secondary outcomes:

1) Migraine intensity: outcomes recording pain intensity using numerical/verbal scale, such as average headache severity per evaluation interval.

2) Responder rate (patients with ≥50% reduction in headache frequency) per evaluation interval.

3) Medication intake used for migraine per evaluation interval.

4) Adverse events, including the number of patients who dropped out due to an adverse event and the number of patients who reported adverse events.

In contrast to a previous meta-analysis of acupuncture for migraine prophylaxis, we define responder rate as a secondary outcome. According to the IHS guideline [34], the responder rate is comparatively insensitive to the treatment effect and particularly vulnerable to selection bias. The responder rate can be evaluated as an important secondary outcome in placebo-controlled RCTs of migraine.

Outcome measurement may be performed at specific time points; the choice will depend on the time when outcomes are reported in the reviewed studies. Specific decisions will be made by the review board.

The following outcome measures will be presented in the 'Summary of findings' table:

1) Migraine frequency.

2) Migraine intensity.

3) Responder rate.

4) Medication use for migraine attacks.

5) Adverse events.

Patient and public involvement

Patient and public involvement will be considered during the whole meta-analysis. We collected the patient's suggestions and comments at both China and Italy for selection of primary, secondary outcome, and conceiving the design of this meta-analysis. As we also have collaborated with Italian Federation of Acupuncture Societies (FISA) to create novel evidence of acupuncture for migraine and established long-term medical collaboration through the European Union's Seventh Framework Programme FP7/2007-2013/ under REA grant agreement number PIRSES-GA-2013-612 589: CHETCH (China and Europe Taking Care of Healthcare solutions), our findings will regularly disseminated to both Chinese and European residents by the local medical institutions.

Search methods for identification of studies

We will conduct our meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [35] and will report this meta-analysis based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and AMED (via OVID) databases as well as four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. No language restriction will be applied. The reference lists of retrieved trials and previous systematic reviews will be searched for citation of potentially eligible trials. We will contact the corresponding author of articles, if any questions about trials arise.

The search strategy for MEDLINE is shown in Table 1.

Table 1 Search strategy to be used in MEDLINE (OVID) database

Number	Search terms
1	Headache Disorders [MeSH]
2	Headache[MeSH]
3	(headache or migraine or cephalgia or cephalalgia or chronic migraine):ti,ab (Word variations have been searched)
4	1 or 2 or 3
5	Acupuncture Therapy [MeSH]
6	(acupuncture or electroacupuncture or electro-acupuncture) :ti,ab
7	5 or 6
8	randomised:ti, ab.
9	randomized:ti,ab.
10	randomly:ti,ab.
11	placebo:ti,ab
12	clinical trials [MeSH]
13	trial ti,ab.
14	randomized controlled trial [MeSH]:ti,ab.
15	randomised controlled trial [MeSH]:ti,ab.
16	controlled clinical trial:ti,ab
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	humans
19	17 and 18

20	4 and 7 and 19

Searching other resources

We will search the US National Institutes of Health Ongoing Trials Register (http://www.clinical trials.gov), the WHO International Clinical Trials Registry Platform (http://www.who.int/trialsearch), and the metaRegister of Controlled Trials (http://www.controlledtrials.com) for any relevant ongoing trials. OpenSIGLE (opensigle.inist.fr) will be searched for conference abstracts. We will also search Google Scholar (scholar.google.com/advanced scholar search?hl=en&lr=) using the search string "acupuncture AND (headache OR migraine OR chronic migraine)" for potential relevant trials from inception to December 31, 2017.

Data collection and analysis

Selection of studies

Two independent reviewers will examine titles and abstracts of the identified studies and will exclude irrelevant trials. When the first selection is made, full articles will be obtained and checked again in more detail. Following this assessment, a second selection will be performed. The criteria for both selections will be extracted and documented. Possible conflicts will be resolved by discussion, which will also include a third reviewer. The selection process will be presented in a PRISMA flow diagram (Figure 1).

Data extraction and coding

Two independent reviewers will extract data from the selected studies using pilot-tested data forms. They include the following study information: author, year of publication, study populations (European ancestry or not), study design, numbers of patients randomized and treated, number of patients analyzed, baseline analysis, random sequence generation, allocation concealment method, blinding method, imputation method, withdrawals of data, interventions, controls, medication records, and primary and secondary outcomes at all reported time points. For investigating the

characteristics of acupuncture effect, we will extract data on age, sex, populations, headache classifications, number and duration of treatment sessions, features of acupuncture treatment (such as type of acupuncture, needle depths, selection of points, achievement of de-chi, manipulation between acupuncture treatment or not), features of control interventions (sham methods, drug use, or standard treatment details), patients' expectations, and experience of acupuncturists in accordance with STRICTA [29].

We also will document for each outcome of interest the percentage of missing values reported in the study.

For the purpose of analyzing the influence of characteristics of acupuncture on its effect size, a coding sheet will be developed to transform all the described data into categorical data. A pilot testing on this coding sheet will be performed on a separate subset of studies. A coding book will be subsequently established to guide the coding process when the code sheet is completed. Two independent reviewers and statisticians will check the coding sheet when coding process has been finished [36].

Assessing risk of bias in included studies

Two reviewers will independently assess the risk of bias for each included RCTs using the Cochrane Collaboration's risk of bias tool [35]. The critical assessment for the risk of bias will be evaluated in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. This assessment will be achieved by assigning a judgement of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias. Because we will only include RCTs using well-described randomization and allocation concealment methods, only those RCTs evaluated as having a low risk of bias for both random sequence generation and allocation concealment will be included. Any disagreement will be resolved by discussion or consensus with a third reviewer. The graphical presentation of assessment of risk of bias will be generated by RevMan V.5.3.5.

Measures of treatment effect

To address the clinical effect difference between the intervention and control

groups, headache frequency at the completion of treatment and at the end of follow-up will be used as a primary outcome. Pain intensity, responder rate, and mediation intake at the completion of treatment and at the end of follow-up also will be extracted as secondary outcomes. For these continuous outcomes, the mean difference (MD) and standard deviations (SDs) will be extracted and calculated as an effect estimate. Negative values will indicate better outcomes in the acupuncture group.

If the MD or SDs were not reported and not available after contacting the authors, we will use the data that are available, such as the median or P values and confidence intervals, and try to re-calculate MD and SD values from the information recorded in the study.

The safety or adverse outcome will be the number of participants who dropped out due to adverse effects and the number of participants who reported at least one adverse event or effect. For these dichotomous outcomes, the odds ratio (OR) will be calculated as the effect estimate. An odds ratio greater than 1 will indicate more events (e.g., dropouts) in the acupuncture group.

For the time window analysis, we will extract outcomes with all the time points using pilot-tested data forms. Subsequently, we will document the quantitative outcomes at the end of treatment together with the length of the treatment period. In a meta-regression, we will adjust treatment effects for time. The R package metafor will allow us to give each outcome a meta-analytic result at different treatment periods. Standard meta-analyses, especially for subgroups, will be performed using the R-package meta [37-38].

Unit of analysis issues

The unit of analysis will be based on aggregated outcome data due to the lack of individual patient data.

Dealing with missing data

If there are insufficient details or missing data related to the characteristics of the studies included for the meta-analysis, we will attempt to contact the study authors for further information at first. For missing participant data due to dropout or loss to follow-up, we will apply the following strategies to address missing data assumed to

be not missing at random:

1) If intention to-treat (ITT) analyses were performed in the included studies, we will use the ITT data instead of missing data as the first option.

2) For continuous missing outcome data, we will try to re-calculate MD and SD values as the first option when the medians, P values or confidence intervals were reported in the included studies.

3) If there are no ITT data or possible data for re-calculation, we will perform a sensitivity analysis to elucidate the influence of missing data on the effect estimates as a second option. This can be performed by a meta-regression adjusting for the amount of missing data.

Assessment of heterogeneity

We will evaluate the heterogeneity of the included studies with I^2 statistic and the tau^2 test. A cutoff point of at least 50% for the I^2 statistic will indicate substantial heterogeneity.

Our second aim is to investigate which clinical setting and which acupuncture features do influence the effect size and the heterogeneity of the intervention. First, we will define characteristics that may modify the intervention effect according to experienced acupuncturists whose have a qualified acupuncture license and at least 10 years of clinical acupuncture experience in accordance with STRICTA [29]. Second, we will examine the correlation between these covariates to exclude possible masking and to establish a core set of covariates. A random-effects meta-regression analysis will be conducted using **metafor** [37] to elucidate the impact of core set covariates on treatment effects.

Before the meta-analysis can be conducted, the relevant results from each study must be quantified in such a way that the resulting values can be further aggregated and compared. Depending on different aspects (goals of the meta-analysis, the design and types of studies included, and the information provided therein), we will calculate the effect size of interest using the **escalc** function.

Subsequently, random/mix-effects of the meta-regression model will be fitted by the **rma()** function [37]. The **restricted maximum-likelihood estimator,** which is an

approximately unbiased and efficient estimator, will be used to address the amount of residual heterogeneity tau^2. The pre-defined covariates (e.g., characteristics of the acupuncturists) will be first fitted independently to examine the possible independent factors contributing to variation in the intervention effect. Subsequently, interaction between covariates (e.g., characteristics of the acupuncturists and session of acupuncture treatment) can be added and detected in the model using the **mods** argument. For the limit of included studies, we will put covariates ≤3 into the same model for each model. For the result interpretation, the **estimate** represents the average effect estimates of covariates, and a P value ≤0.05 represents a significant difference that indicates the corresponding covariate plays an important role for the intervention effect and heterogeneity. In addition, the amount of heterogeneity in the effect estimate will be estimated by **tau^2**. The $\mathbf{I^2}$ statistic estimates (in percent) how much of the total variability in the effect size estimate (which is composed of heterogeneity and sampling variability) can be attributed to heterogeneity among the true effects. The results of the meta-regression outlined above will be presented in a series of summary tables in the meta-analysis.

Assessment of reporting biases

Reporting bias will be explored by constructing funnel plots and performing Egger's test, if there are at least 10 trials included in meta-analysis.

Data synthesis

The synthesis will be done by generating a forest plot for meta-regression. This plot does not contain a summary measure given by a prism below the single studies, but by a prism shown for each single study that shows the aggregated effect for the specific type of study (depending on the covariates of the meta-regression). If the heterogeneity test indicates there is no substantial heterogeneity between studies, the Mantel-Haenszel method implemented by the **rma.mh()** function will be fitted for calculating pooled estimates, 95% confidence intervals, and combined P values. If substantial heterogeneity is indicated by $I^2 \geq 50\%$, the random-effects model will be performed by the DerSimonian and Laird method (DerSimonian 1986) and the **rma** function. The significance of the P value represents the strength of evidence against

the null hypothesis of no intervention effect.

Subgroup analysis

Subgroup analysis will be performed according to the primary and secondary objectives. To detect possible heterogeneity of the results, subgroup analysis will be conducted for both the primary outcome and secondary outcomes at the end of the treatment session and the end of the follow-up period. We will investigate the effects for four subgroup analyses:

1) episodic migraine vs. chronic migraine
2) acupuncture vs. different type of sham acupuncture and controls
3) Western studies vs. Chinese studies
4) early time-point of outcomes vs. later time-point of outcomes

In addition, if we detect any important and significant covariates contributing to the variation of the intervention effect by meta-regression, subgroup analyses will also be conducted according to these covariates.

Sensitivity analysis

To confirm the robustness of our findings, a sensitivity analysis will be conducted based on the different levels of bias of the included studies. To evaluate the internal validity of studies or treatment adequacy, we will subsequently remove studies of 'high risk' of bias, studies of 'unclear risk' of bias, and studies of 'low risk' of bias using the **metafor** package and **leave1out()** function.

Summary of evidence

We will summarize the quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [39] and present 'Summary of findings' tables. The 'Summary of findings' tables will be generated by the GRADE working group software (GRADEpro or GRADEpro GDT [www.gradepro.org]). The content of the 'Summary of findings' tables (main outcomes that are important to patients and decision makers) will be determined by the review group described above. Where possible, both relative and absolute measures of effect will be provided. To assess the quality of evidence, the GRADE approach evaluates the quality of evidence as 'high', 'moderate', 'low', or 'very low' by outcome. Evidence can be downgraded in category by concerns about risk of bias,

imprecision, inconsistency, indirectness, or publication bias, and also can be upgraded by a large effect size, plausible confounding that could change the effect size, and dose-response relation. Reviewers will downgrade or upgrade the evidence according to the GRADE guideline in the Cochrane handbook, Chapter 11 [35] and also take into account the differences in anticipated effects in the group of primary interest. The total quality of evidence will decided by not only the reviewers but also based on the opinion of patients, decision makers, and acupuncturists. The whole summarization of the evidence process will be succinct and transparent.

Ethics and dissemination

The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data that will be used will not contain individual patient data; therefore, ethical approval is not required, and there is no concerns about patient's privacy.

Discussion

This meta-analysis will not only evaluate evidence from published RCTs for the effectiveness of acupuncture in treating both episodic migraine and chronic migraine, but also will detect possible characteristics that influence the main effect and the specific effect of acupuncture for migraine. This will be achieved by using meta-regression. We hope that using meta-regression techniques in this meta-analysis will not only provide a deeper understanding of the effect of acupuncture in patients with migraine but also generate evidence for factors that modify the effect, which will support the optimization of acupuncture treatment for migraine in the pragmatic clinical setting. If this protocol must be amended, we will present the date of each amendment with a description of the change and the corresponding rationale.

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Author Contributions

UM is the guarantor. ZG, UM, CG and ZX contributed to the conception of the study. The manuscript presenting the protocol was drafted by ZG and revised by UM. The search strategy was developed by all authors and will be run by ZG and HL, who will also independently screen the potential studies, extract data from included studies, assess the risk of bias. ZG and UM will conduct and finish the data synthesis. LQ and CH will arbitrate in cases of disagreement and ensure no errors occur during the study. All authors have approved the publication of the protocol.

Competing interests

None declared

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Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement: Technical appendix, statistical code and data set are available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the data set.

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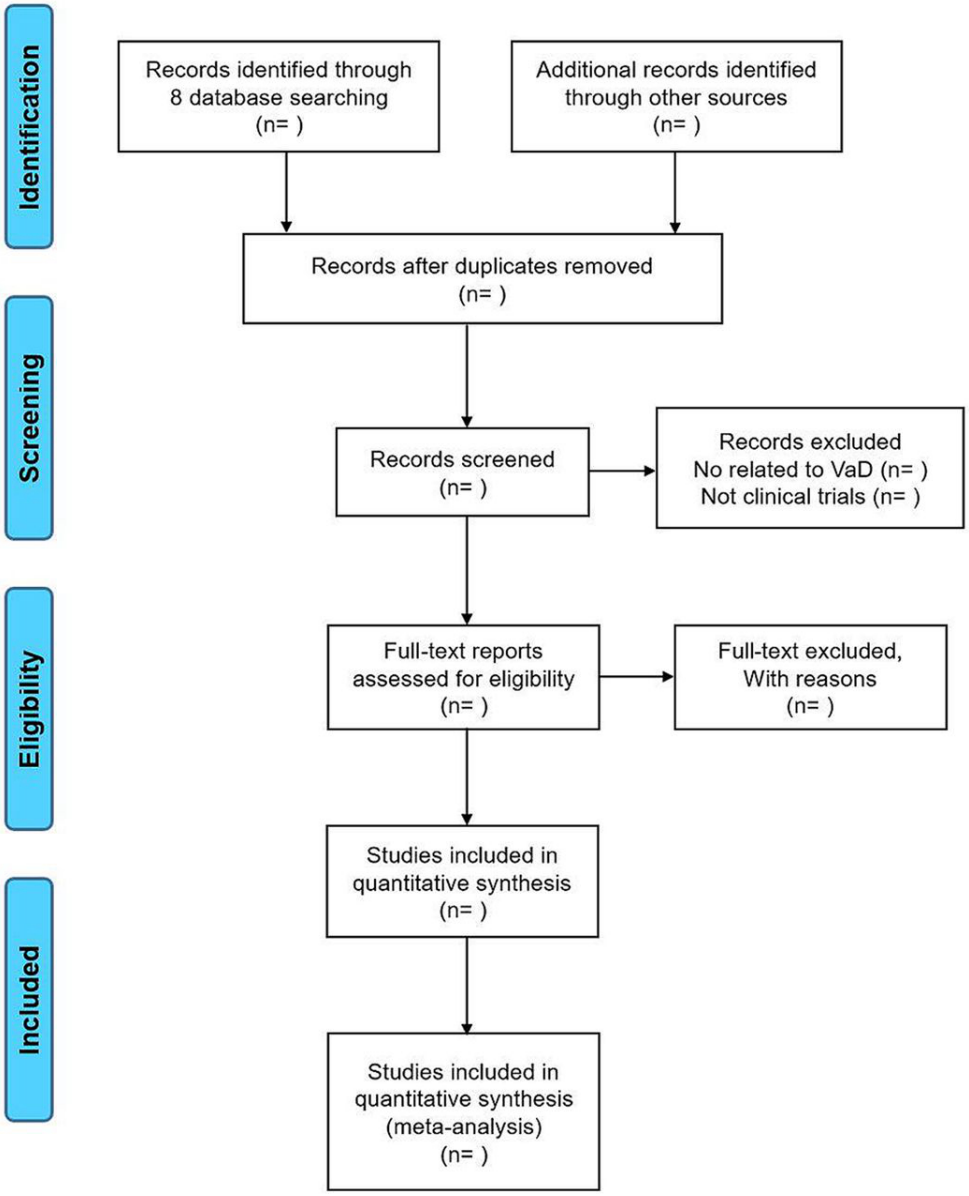
FIGURES

FIGURE 1. Prisma 2009 flow diagram



Prisma_2009_flow_diagram

88x108mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	18
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19
	#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	18

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	19
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	19
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7-10
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	11
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	12
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13
Study records - 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)	13
Study records - 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	13
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	13

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	14
	#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 I2, Kendall's τ)	14-15
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16-17
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17

BMJ Open

Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022998.R2
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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Acupuncture, Meta analysis protocol, Meta regression, Migraine < NEUROLOGY

Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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ABSTRACT

Introduction

Although the effectiveness of acupuncture for episodic migraine has been confirmed by multiple clinical trials and Cochrane systematic reviews, the mechanisms underlying the specific effect of acupuncture for migraine remain controversial. We aim to evaluate the effectiveness and safety of acupuncture for both episodic migraine and chronic migraine by meta-analysis and explore the possible factors influencing the specific effect of acupuncture for migraine by meta-regression.

Methods and analysis

We will search for randomized control trials (RCTs) of acupuncture for migraine in the following eight databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED (via OVID), and four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. We will also search OpenSIGLE (opensigle.inist.fr) for conference abstracts. No language restriction will be applied. The selection of studies, data extraction and coding, and assessment of risk of bias of the included studies will be conducted independently by two reviewers. Standard meta-analysis and, if appropriate, meta-regression will be performed using the R packages Meta and Metafor.

Ethics and dissemination

The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data used in this meta-analysis will not contain individual patient data; therefore, ethical approval is not required.

Trial registration number: PROSPERO CRD42018087270.

Keywords: acupuncture; migraine; meta-regression; meta-analysis

Strengths and limitations of this study

1. This meta-analysis will not only evaluate the effectiveness of acupuncture in treating both episodic migraine and chronic migraine but also will detect possible characteristics that influence the main effect and the specific effect of acupuncture for migraine.

2. Equipped with advanced machine learning techniques and R packages Meta and Metafor, this meta-analysis could uniquely explore the interaction and combinatory effects of different clinical factors that may affect the main effect and specific effect of acupuncture for migraine.

3. The results of this meta-analysis may reveal pivotal factors that impact the clinical effect of acupuncture, and thus, will support the optimization of acupuncture treatment for migraine in the pragmatic clinical setting.

4. Electronic databases for Korean and Japanese studies will not be searched. Therefore, language bias may exist.

Introduction

Description of the condition

Migraine is one of the most common headache disorders and is characterized by recurrent unilateral, throbbing, moderate-to-severe attacks of headache lasting from 4–72 h, with or without aura [1]. Migraine is commonly associated with symptoms of nausea, vomiting, photophobia and phonophobia, and is aggravated by physical exertion. According to the 2010 Global Burden of Disease Survey, migraine ranked as the third most predominant disorder, as well as the seventh highest specific cause of disability worldwide. In the US, an estimated 36 million individuals experience migraine attacks, with approximately 16%–18% of women and 6%–8% of men suffering recurrent migraine attacks during their professional lives [2–3]. Migraine usually can be categorized as episodic migraine (migraine attacks happening fewer than 15 days each month) and chronic migraine (migraine attacks happening more than 15 days per month) [1]. Two large population-based studies documented a strong tendency for episodic migraine to evolve into chronic migraine, often associated with overuse of

analgesics [4]. Further, a systematic review focusing on the global prevalence of migraine reported that the prevalence of chronic migraine is 0–5.1%, with estimates typically among 1.4–2.2% [5]. Recently, many studies also demonstrated a correlation between migraine and cardiovascular and cerebrovascular diseases [6-7]. A systematic review investigating migraine and cardiovascular disease found that the risk of ischemic stroke was doubled in people who had migraine with aura [8]. It is well accepted that migraine with aura is associated with ischemic stroke in younger women (age≤45 years) [9].

Description of the intervention

To be considered effective, treatments for migraine should reduce the occurrence of migraine attacks and relieve symptoms in order to improve patients' quality of life and decrease related healthcare utilization. Pharmacological agents for migraine are widely used to reduce migraine attack frequency and pain intensity, including propranolol, metoprolol, flunarizine, valproic acid, and topiramate [10]. Unlike acute migraine that can often be managed with drugs, chronic migraine is difficult to control due to the frequency of attacks and overuse of drugs among migraine patients [5]. Furthermore, pharmacological treatment for migraine with oral nonsteroidal anti-inflammatory drugs (NSAIDS) and tripans has a modest effect and often leads to several side effects, such as gastrointestinal and cardiovascular disorders [11]. Thus, there is a strong need for the development and implementation of additional long-term effective, low-risk treatments for migraine.

Acupuncture is a procedure whereby fine needles are inserted into and manipulated within the skin of acupoints at certain depths to reduce symptoms and achieve curing of diseases [12]. Acupuncture originated in China within the Chinese civilization and has become one of the most widely used forms of Traditional Chinese Medicine (TCM). The treatment effect of acupuncture is regarded as balancing the disorder within the human body in order to treat diseases. Such balancing is achieved by activating accurate meridians and acupoints of the body using diverse needling techniques, according to disease and personal status. Currently, even without a clear

understanding of underlying mechanisms, acupuncture has been extensively used for migraine prophylaxis and chronic pain treatment worldwide. According to a survey in the US, 9.9% of patients who received acupuncture treatment did so in search of relief from migraine and other headaches [13]. A 2016 Cochrane Review from Germany concluded that acupuncture is safe and effective for episodic migraine prophylaxis compared to prophylactic drug treatment [14].

How the intervention might work

While enhanced calcitonin gene-related peptide (CGRP) and spontaneous cortical spreading depression (CSD) are regarded as causative in triggering migraine [15], the pathophysiology of migraine is attributed to multiple factors, and many of which remain unclear. Recently, an increasing number of studies have confirmed that acupuncture activates the release of opioid peptides in the central nervous system (CNS). Release of these peptides corresponds to long-lasting activation of ascending sensory tracks, thereby relieving an array of pain conditions [16-19]. Furthermore, Zhao et al. confirmed in a migraine rat model that electro-acupuncture treatment can depress CGRP expression in the trigeminal ganglion, which plays a key role in inducing migraine attack [20]. Li et al. also found that acupuncture restores the impaired descending pain modulatory system (DPMS) in migraine patients by decreasing the resting state functional connectivity (rs-fc) between the periaqueductal gray (PAG) and rostral anterior cingulate cortex/medial prefrontal cortex (rACC/mPFC), which directly correlated with the intensity of pain during the migraine attack [21].

In contrast to the conflicting evidence concerning the mechanism by which acupuncture relieves migraine, evidence of the effectiveness of acupuncture for migraine was provided by a series of Cochrane systematic reviews and a large individual patient meta-analysis [14, 22]. However, the concept of a “placebo effect” and “specific effect” regarding the clinical effect of acupuncture for migraine is still controversial [22]. An updated Cochrane review of acupuncture for episodic migraine concluded that acupuncture is an effective treatment for the prevention of migraine, but on the other hand, the difference in the effect size between acupuncture and sham

acupuncture was relatively small [14]. Linde et al. argued that understanding the specific effect of acupuncture is essential for the acceptance of acupuncture as a legitimate treatment in Western countries. Therefore, evidence confirming the specific effect of acupuncture is still in high demand for biomedicine [23]. Nevertheless, key components of the effect of acupuncture remain to be fully uncovered. Accordingly, designing appropriate sham acupuncture as a placebo control is still a difficulty for clinical acupuncture trials. Thus, this debated issue may be an obstacle to the acceptance of acupuncture as a valid therapy in pain management by both Western scientific researchers and policy makers.

Why it is important to do this review

To investigate the effect and specificity of acupuncture, a newly updated Individual Patient Data Meta-Analysis of acupuncture for chronic pain [24] concluded that true acupuncture has a long-term effect compared with sham acupuncture. Nevertheless, it also pinpointed that characteristics of acupuncture treatment sessions contribute to the effect of acupuncture, in addition to the specific effects of needling. However, this meta-analysis mainly focused on chronic pain and chronic headache and was not specific to migraine. There is still insufficient evidence to elucidate the specific mechanism of the effect of acupuncture for migraine. Furthermore, a recent German Cochrane Review [14] demonstrated the effectiveness of acupuncture in the prevention of episodic migraine. Whereas, there has been no systematic review of the effect of acupuncture in the prevention of chronic migraine. Therefore, three pivotal questions arise from the former meta-analysis and clinical studies of acupuncture for migraine: i) is acupuncture an effective therapy for both episodic migraine and chronic migraine in the clinical setting? ii) are there any important factors that influence the effect of acupuncture? and iii) are there any features that alter the specific effect of acupuncture compared with sham acupuncture or other controls in clinical acupuncture treatment for migraine? To address these critical questions, we will conduct a meta-analysis of RCTs of acupuncture for migraine.

Objective

This meta-analysis in adults with episodic or chronic migraine aims to assess:

1. The effectiveness and safety of acupuncture compared to sham acupuncture and drug treatment or waiting list controls in the prevention of migraine;

2. The features that may contribute to: i) different effect sizes between acupuncture and controls, ii) the specific effect of acupuncture, iii) the non-specific effects of sham acupuncture or other controls, and to identify iv) which factors among all those studied most strongly influence the effect of acupuncture.

Methods

Criteria for considering studies for this review

Types of studies

We will only include RCTs investigating the effect of acupuncture on episodic and chronic migraine in adults [4]. We will only include RCTs (parallel groups as well as cross-over) using well-described randomization methods.

We will exclude quasi-randomized clinical trials.

Types of participants

We will include patients of either sex with an age aged 18 and older, who have been diagnosed either with episodic or chronic migraine. Migraine diagnoses must be based on the International Headache Society (ICHD-III beta 2013 and its previous editions ICHD-II 2004; IHS1988) and the Ad Hoc Committee on the Classification of Headache (Ad Hoc 1962) [25-28]. If no specified criteria were documented in the studies, the migraine diagnosis must be based on discriminable and important characteristics of migraine attacks (e.g., recurrent headache, unilateral pain, pulsating quality, moderate or severe intensity, in association with nausea and/or photophobia and phonophobia), as confirmed by patients' doctors or general practitioners. In general, episodic migraine occurs in two to eight episodes but with migraine attacks less than 15 days per month, whereas chronic migraine patients usually suffer migraine attacks at least 15 days per month (180 days per year) for at least 3 months [1].

The duration of migraine history must be longer than 1 year in the majority of

patients. This criterion will be considered met if:

1) An explicit description of the duration of migraine history longer than 1 year is noted in the inclusion criteria;

2) The mean duration minus one standard deviation is longer than 1 year as shown in the table of baseline characteristics; or

3) Other information confirms that the criterion was met (e.g., proportions with duration ranges are presented in the studies).

We will include studies in which patients were defined as having 'combination' or 'mixed' migraine only if we can extract the data on participants affected with migraine.

We will exclude trials including patients with secondary headache. Studies including chronic migraine patients with medication-overuse history (according to the International Classification of Headache Disorders, 3rd beta edition (ICHD-IIIß) criteria [25]) will also be excluded.

Types of intervention

Experimental intervention

We define acupuncture (both manual and electrical stimulation) as the experimental intervention. Acupuncture is defined as insertion of specific needles into the skin of the body at selected acupoints (defined as 'meridian acupoints', which belong to 14 meridians in the body according to traditional acupuncture theory), pain points (defined as 'a-shi points' in the location of pain condition according to traditional acupuncture theory), or extraordinary points (defined as 'extra points', which do not belong to the 14 meridians but have a therapeutic effect in the body according to traditional acupuncture theory) up to definite therapeutic depths. In accordance with a previous Cochrane systematic review of acupuncture for migraine [14], the dosage of acupuncture treatment must be at least six treatment sessions, with a duration of at least 20 minutes per session and at least one session per week in the majority of patients. Also, for the purpose of ensuring the clinical effectiveness of acupuncture treatment, the acupuncturists who administered treatment in the included studies should be confirmed to have a relevant acupuncture qualification or professional affiliation, or a certain number of years in acupuncture practice. In addition, trials that define

acupuncture in combination with other pharmacological treatment or physical treatment as the experimental intervention but mainly investigate the effectiveness of acupuncture will also be included.

As this meta-analysis will mainly focus on the effectiveness of acupuncture on the basis of traditional acupuncture theory and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [29], we will exclude trials in which:

1) Acupuncture was performed at one specific body area but not at acupoints of the body, such as scalp acupuncture, ear acupuncture, and wrist-ankle acupuncture.

2) Acupoints were stimulated by other techniques without traditional acupuncture needling, including acupressure, laser stimulation, injection acupuncture, dry needling, and trigger point therapy.

Control interventions

We will include three types of control interventions:

1) No treatment or waiting list-control during the trial period.

2) Sham acupuncture (intervention resembling verum acupuncture treatment but using superficial needle insertion, needle insertion at non-acupuncture points or at points not indicated for the condition under study, and 'placebo' needles that seem to be inserted into skin but actually are not [30-33], etc). Trials which have intervention groups that compared either acupuncture alone with sham intervention alone or acupuncture plus one or more therapies with sham intervention plus the same therapies also will be included.

3) Pharmacological treatment that is given as a control during a comparable time as application of acupuncture treatment.

Because our objective is to evaluate the effectiveness of acupuncture treatment compared to sham acupuncture treatment, no treatment, or western medicine treatment, we will exclude trials with herbal medicine, moxibustion, bloodletting, and other different forms of acupuncture as control interventions.

Types of outcome measures

To be considered for inclusion, trials must have evaluated at least one of the following primary efficacy outcome measures [34] for at least 4 weeks from the

beginning of acupuncture treatment:

1) Number of migraine attacks per evaluation interval;

2) Number of migraine days per evaluation interval;

Before the review process, a review board consisting of an epidemiologist, acupuncturist, migraine patient, social policymakers, and statistician will be established to determine all the key outcomes, with respect of migraine patients' opinions and values.

We will exclude studies that:

1) Included primary outcome measurements only using "effectiveness rate";
2) Exclusively used objective or surrogate outcome measures;
3) Evaluated treatment or measurement of acute migraine attack;
4) Had outcome evaluation periods shorter than 4 weeks (after randomization to end of treatment).

According to the guidelines for controlled trials of drugs in migraine published by the IHS [34], the main outcomes will be:

Primary outcome:

Migraine frequency:

We will consider the following outcomes measuring headache frequency:

1） Numbers of migraine attacks per evaluation interval;

2）Number of migraine days per evaluation interval.

Secondary outcomes:

1) Migraine intensity: outcomes recording pain intensity using numerical/verbal scale, such as average headache severity per evaluation interval.

2) Responder rate (patients with≥50% reduction in headache frequency) per evaluation interval.

3) Medication intake for migraine per evaluation interval.

4) Adverse events, including the number of patients who dropped out due to an adverse event and the number of patients who reported adverse events.

In contrast to a previous meta-analysis of acupuncture for migraine prophylaxis, we define responder rate as a secondary outcome. According to the IHS guideline [34], the

responder rate is comparatively insensitive to the treatment effect and particularly vulnerable to selection bias. The responder rate can be evaluated as an important secondary outcome in placebo-controlled RCTs of migraine.

Outcome measurement may be performed at specific time points; the choice will depend on the time when the outcomes are reported in the reviewed studies. Specific decisions will be made by the review board.

The following outcome measures will be presented in the 'Summary of findings' table:

1) Migraine frequency.

2) Migraine intensity.

3) Responder rate.

4) Medication use for migraine attacks.

5) Adverse events.

Patient and public involvement

Patient and public involvement will be considered during the entire meta-analysis. We collected patients' suggestions and comments from both China and Italy for the selection of outcomes and design of this meta-analysis. In addition, we will collaborate with the Italian Federation of Acupuncture Societies (FISA) to collect novel evidence for the application of acupuncture for migraine and establish a long-term medical collaboration through the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement number PIRSES-GA-2013-612 589: CHETCH (China and Europe Taking Care of Healthcare solutions). Thus, our findings will be regularly disseminated to both Chinese and European residents by the local medical institutions.

Search methods for identification of studies

We will conduct our meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [35] and will report this meta-analysis based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and AMED (via OVID) databases as well as four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. No language restriction will be applied. The reference lists of retrieved trials and previous systematic reviews will be searched for citation of potentially eligible trials. We will contact the corresponding author of articles, if any questions about trials arise.

The search strategy for MEDLINE is shown in Table 1.

Table 1 Search strategy to be used in MEDLINE (OVID) database

Number	Search terms
1	Headache Disorders [MeSH]
2	Headache[MeSH]
3	(headache or migraine or cephalgia or cephalalgia or chronic migraine):ti,ab (Word variations have been searched)
4	1 or 2 or 3
5	Acupuncture Therapy [MeSH]
6	(acupuncture or electroacupuncture or electro-acupuncture) :ti,ab
7	5 or 6
8	randomised:ti, ab.
9	randomized:ti,ab.
10	randomly:ti,ab.
11	placebo:ti,ab
12	clinical trials [MeSH]
13	trial ti,ab.
14	randomized controlled trial [MeSH]:ti,ab.
15	randomised controlled trial [MeSH]:ti,ab.
16	controlled clinical trial:ti,ab
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	humans
19	17 and 18
20	4 and 7 and 19

Searching other resources

We will search the US National Institutes of Health Ongoing Trials Register (http://www.clinical trials.gov), the WHO International Clinical Trials Registry Platform (http://www.who.int/trialsearch), and the metaRegister of Controlled Trials (http://www.controlledtrials.com) for any relevant ongoing or unpublished trials.

OpenSIGLE (opensigle.inist.fr) will be searched for conference abstracts. We will also search Google Scholar (scholar.google.com/advanced scholar search?hl=en&lr=) using the search string "acupuncture AND (headache OR migraine OR chronic migraine)" for potentially relevant trials from inception to December 31, 2017.

Data collection and analysis

Selection of studies

Two independent reviewers will examine titles and abstracts of the identified studies and will exclude irrelevant trials. When the first selection is made, full articles will be obtained and checked again in more detail. Following this assessment, a second selection will be performed. The criteria for both selections will be extracted and documented. Possible conflicts will be resolved by discussion, which will also include a third reviewer. The selection process will be presented in a PRISMA flow diagram (Figure 1).

Data extraction and coding

Two independent reviewers will extract data from the selected studies using pilot-tested data forms. They will include the following study information: author, year of publication, study populations (European ancestry or not), study design, numbers of patients randomized and treated, number of patients analyzed, baseline analysis, random sequence generation, allocation concealment method, blinding method, imputation method, withdrawals of data, interventions, controls, medication records, and primary and secondary outcomes at all reported time points. For investigating the characteristics of acupuncture effect, we will extract data on age, sex, populations, headache classifications, number and duration of treatment sessions, features of acupuncture treatment (such as type of acupuncture, needle depths, selection of points, achievement of de-chi, manipulation between acupuncture treatment or not), features of control interventions (sham methods, drug use, or standard treatment details), patients' expectations, and experience of acupuncturists in accordance with STRICTA [29].

We also will document for each outcome of the percentage of missing values reported in the study.

For the purpose of analyzing the influence of characteristics of acupuncture on its effect size, a coding sheet will be developed to transform all the described data into categorical data. Pilot testing on this coding sheet will be performed on a separate subset of studies. A coding book will be subsequently established to guide the coding process when the code sheet is completed. Two independent reviewers and statisticians will check the coding sheet when coding process has been finished [36].

Assessing risk of bias in included studies

Two reviewers will independently assess the risk of bias for each included RCTs using the Cochrane Collaboration's risk of bias tool [35]. The critical assessment for the risk of bias will be evaluated in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. This assessment will be achieved by assigning a judgement of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias. Because we will only include RCTs using well-described randomization and allocation concealment methods, only those RCTs considered to have a low risk of bias for both random sequence generation and allocation concealment will be included. Any disagreement will be resolved by discussion or consensus with a third reviewer. The graphical presentation of assessment of risk of bias will be generated by RevMan V.5.3.5.

Measures of treatment effect

To address the clinical effect difference between the intervention and control groups, headache frequency at the completion of treatment and at the end of follow-up will be used as a primary outcome. Pain intensity, responder rate, and mediation intake at the completion of treatment and at the end of follow-up also will be extracted as secondary outcomes. For these continuous outcomes, the mean difference (MD) and standard deviations (SDs) will be extracted and calculated as an effect estimate. Negative values will indicate better outcomes in the acupuncture group.

If the MD or SDs were not reported and not available after contacting the authors, we will use the data that are available, such as the median or P values and confidence intervals, and try to re-calculate MD and SD values from the information recorded in

the study.

The safety or adverse outcome will be the number of participants who dropped out due to adverse effects and the number of participants who reported at least one adverse event or effect. For these dichotomous outcomes, the odds ratio (OR) will be calculated as the effect estimate. An odds ratio greater than 1 will indicate more events (e.g., dropouts) in the acupuncture group.

For the time window analysis, we will extract outcomes with all the time points using pilot-tested data forms. Subsequently, we will document the quantitative outcomes at the end of treatment together with the length of the treatment period. In a meta-regression, we will adjust treatment effects for the time. The R package metafor will allow us to give each outcome a meta-analytic result at different treatment periods. Standard meta-analyses, especially for subgroups, will be performed using the R-package meta [37-38].

Unit of analysis issues

The unit of analysis will be based on aggregated outcome data due to the lack of individual patient data.

Dealing with missing data

If there are insufficient details or missing data in relation to the characteristics of the studies included in the meta-analysis, we will attempt to contact the study authors for further information first. For missing participant data due to dropout or loss to follow-up, we will apply the following strategies to address missing data assumed to be not missing at random:

1) If intention to-treat (ITT) analyses were performed in the included studies, we will use the ITT data instead of missing data as the first option.

2) For continuous missing outcome data, we will try to re-calculate MD and SD values as the first option when the medians, P values or confidence intervals are reported in the included studies.

3) If there are no ITT data or possible data for re-calculation, we will perform a sensitivity analysis to elucidate the influence of missing data on the effect estimates as a second option. This can be performed by a meta-regression adjusting for the amount

of missing data.

Assessment of heterogeneity

We will evaluate the heterogeneity of the included studies with I^2 statistic and the tau^2 test. A cutoff point of at least 50% for the I^2 statistic will indicate substantial heterogeneity.

Our second aim is to investigate which clinical setting and which acupuncture features do influence the effect size and the heterogeneity of the intervention. First, we will define characteristics that may modify the intervention effect according to experienced acupuncturists. These acupuncturists are required to have a qualified acupuncture license and at least 10 years of clinical acupuncture experience in accordance with STRICTA [29]. Second, we will examine the correlation between these covariates to exclude possible masking and to establish a core set of covariates. A random-effects meta-regression analysis will be conducted using **metafor** [37] to elucidate the impact of core set covariates on treatment effects.

Before the meta-analysis can be conducted, the relevant results from each study must be quantified in such a way that the resulting values can be further aggregated and compared. Depending on different aspects (goals of the meta-analysis, the design and types of studies included, and the information provided therein), we will calculate the effect size of interest using the **escalc** function.

Subsequently, random/mix-effects of the meta-regression model will be fitted by the **rma()** function [37]. The **restricted maximum-likelihood estimator,** which is an approximately unbiased and efficient estimator, will be used to address the amount of residual heterogeneity tau^2. The pre-defined covariates (e.g., characteristics of the acupuncturists) will be first fitted independently to examine the possible independent factors contributing to variation in the intervention effect. Subsequently, interaction between covariates (e.g., characteristics of the acupuncturists and session of acupuncture treatment) can be added and detected in the model using the **mods** argument. For the limit of included studies, we will put covariates≤3 into the same model for each model. For the result interpretation, the **estimate** represents the average effect estimates of covariates, and a P value≤0.05 represents a significant difference

that indicates the corresponding covariate plays an important role for the intervention effect and heterogeneity. In addition, the amount of heterogeneity in the effect estimates will be estimated by **tau^2**. The $\mathbf{I^2}$ statistic estimates (in percent) how much of the total variability in the effect size estimate (which is composed of heterogeneity and sampling variability) can be attributed to heterogeneity among the true effects. The results of the meta-regression outlined above will be presented in a series of summary tables in the meta-analysis.

Assessment of reporting biases

Reporting bias will be explored by constructing funnel plots and performing Egger's test, if there are at least 10 trials included in meta-analysis.

Data synthesis

The synthesis will be done by generating a forest plot for meta-regression. This plot does not contain a summary measure given by a prism below the single studies, but by a prism shown for each single study that shows the aggregated effect for the specific type of study (depending on the covariates of the meta-regression). If the heterogeneity test indicates there is no substantial heterogeneity between studies, the Mantel-Haenszel method implemented by the **rma.mh()** function will be fitted for calculating pooled estimates, 95% confidence intervals, and combined P values. If substantial heterogeneity is indicated by $I^2 \geq 50\%$, the random-effects model will be performed by the DerSimonian and Laird method (DerSimonian 1986) and the **rma** function. The significance of the P value represents the strength of evidence against the null hypothesis of no intervention effect.

Subgroup analysis

Subgroup analysis will be performed according to the primary and secondary objectives. To detect possible heterogeneity of the results, subgroup analysis will be conducted for both the primary outcome and secondary outcomes at the end of the treatment session and the end of the follow-up period. We will investigate the effects in four subgroup analyses:

1) Episodic migraine vs. chronic migraine
2) Acupuncture vs. different type of sham acupuncture and controls
3) Western studies vs. Chinese studies

4) Early time-point of outcomes vs. later time-point of outcomes

In addition, if we detect any important and significant covariates contributing to the variation of the intervention effect by meta-regression, subgroup analyses will also be conducted according to these covariates.

Sensitivity analysis

To confirm the robustness of our findings, a sensitivity analysis will be conducted based on the different levels of bias of the included studies. To evaluate the internal validity of studies or treatment adequacy, we will subsequently remove studies of 'high risk' of bias, studies of 'unclear risk' of bias, and studies of 'low risk' of bias using the **metafor** package and **leave1out** function.

Summary of evidence

We will summarize the quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [39] and present 'Summary of findings' tables. The 'Summary of findings' tables will be generated by the GRADE working group software (GRADEpro or GRADEpro GDT [www.gradepro.org]). The content of the 'Summary of findings' tables (main outcomes that are important to patients and decision makers) will be determined by the review group described above. Where possible, both relative and absolute measures of effect will be provided. To assess the quality of evidence, the GRADE approach evaluates the quality of evidence as 'high', 'moderate', 'low', or 'very low' by the outcome. Evidence can be downgraded in category by concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias, and also can be upgraded by a large effect size, plausible confounding that could change the effect size, and dose-response relation. Reviewers will downgrade or upgrade the evidence according to the GRADE guideline in the Cochrane handbook, Chapter 11 [35] and also take into account the differences in anticipated effects in the group of primary interest. The total quality of the evidence will be on the basis of both reviewers and all the members of the review board.

Ethics and dissemination

The results of this meta-analysis and meta-regression will be disseminated through

publication in a peer-reviewed journal and be presented at a relevant conference. The data that will be used will not contain individual patient data; therefore, ethical approval is not required, and there are no concerns about patients' privacy.

Discussion

This meta-analysis will not only evaluate the evidence from published RCTs for the effectiveness of acupuncture in treating both episodic migraine and chronic migraine, but also will detect possible characteristics that influence the main effect and the specific effect of acupuncture for migraine. This will be achieved by using meta-regression. We hope that using meta-regression techniques in this meta-analysis will not only provide a deeper understanding of the effect of acupuncture in patients with migraine, but also generate evidence for factors that modify the effect, which will support the optimization of acupuncture treatment for migraine in the pragmatic clinical setting. If this protocol must be amended, we will present the date of each amendment with a description of the change and the corresponding rationale.

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Author Contributions

UM is the guarantor. ZG, UM, CG and ZX contributed to the conception of the study. The manuscript presenting the protocol was drafted by ZG and revised by UM. The search strategy was developed by all authors and will be run by ZG and HL, who will also independently screen the potential studies, extract data from included studies, and assess the risk of bias. ZG and UM will conduct and finish the data synthesis. LQ and CH will arbitrate in cases of disagreement and ensure no errors occur during the study. All authors have approved the publication of the protocol.

Competing interests

None declared

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Data sharing statement A technical appendix, the statistical code, and the data set are available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the data set.

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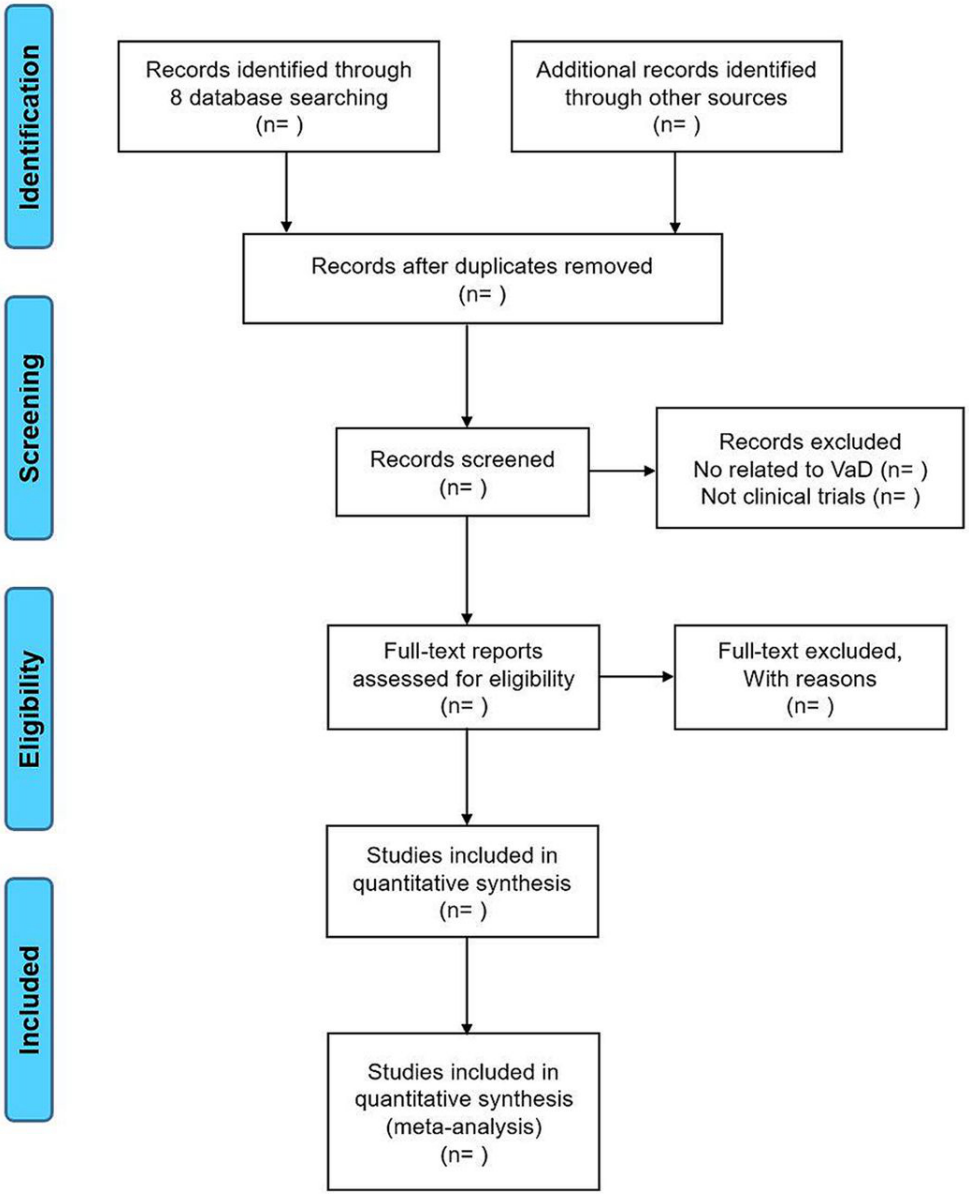
FIGURES

FIGURE 1. Prisma 2009 flow diagram



Prisma_2009_flow_diagram

88x108mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	18
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19
	#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	18

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	19
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	19
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7-10
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	11
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	12
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13
Study records - 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)	13
Study records - 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	13
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	13

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	14
	#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 I2, Kendall's τ)	14-15
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16-17
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17