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Title: Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Knee osteoarthritis is one of the leading causes of disability. The effectiveness of acupuncture for treating KOA remains controversial. This protocol describes the method of a systematic review and meta-analysis evaluating the efficacy and safety of acupuncture for treating KOA.

Methods and analysis

Four English databases (PubMed, Embase, Cochrane Library databases, and Web of Science) and four Chinese databases (China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, and Wanfang) will be searched from the database inception to September 1, 2021. All randomized controlled trials related to acupuncture for KOA will be included. Extracted data will include publication details, basic information, demographic data, intervention details and patient outcomes. The primary outcome is pain intensity. Risk of bias will be assessed using the Cochrane Collaboration's tool for assessing risk of bias. Article selection, data extraction and risk of bias assessment will be performed in duplicate by two independent reviewers. If the meta-analysis is precluded, we will conduct a descriptive synthesis using a best-evidence synthesis approach. The strength of recommendations and quality of evidence will be assessed using the Grading of Recommendations Assessment Development and Evaluation working group methodology.

Ethics and dissemination

Ethics approval is not required because individual patient data are not included. This protocol was registered in the international Prospective Register of Systematic Reviews on 25 February 2021. The systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal. The findings will also be disseminated through conference presentations.

Trial registration number

CRD42021232177

Article summary

Strengths and limitations of this study

1. This study will be the first of its kind to explore the difference in the efficacy between manual acupuncture and electroacupuncture for KOA by synthesizing the evidence from direct comparison and indirect comparison.

2. We want to focus on many different factors in subgroup analysis and to explore the applied law of different doses of acupuncture.

3. The study design adheres to all relevant guidelines for systematic reviews and meta-analyses.

4. We plan to search multiple Chinese and English language databases to ensure a comprehensive search of the literature.

5. Transformation of pain scores will result in loss of some accuracy; however, we believe that it is clinically irrelevant.

INTRODUCTION

Description of the condition

Osteoarthritis (OA) is a common clinical degenerative disease and is one of the leading causes of disability.[1] The costs of OA are considerable, estimated at between 1% and 2.5% of the gross domestic product for Western countries.[2] The knee is the most common location of osteoarthritis, which accounts for approximately 85% of osteoarthritis cases worldwide.[3] With the trends of an aging population and increasing obesity, the incidence of knee osteoarthritis (KOA) is increasing for both sexes.[4 5] In addition, pain symptoms associated with KOA result in physical and walking disability, which in turn have an excess risk of all-cause mortality. [6 7]

Exercise and weight loss, two effective nonpharmacological treatments, are strongly recommended in all people with clinical osteoarthritis.[8] However, for patients with KOA, it is difficult to continue exercising and losing weight. Representatives of pharmacological interventions include analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). However, some analgesics are not associated with long-term pain improvement and have nearly no effects at various doses.[9 10] Furthermore, many NSAIDs are associated with serious side effects such as cardiovascular and renal adverse effects, gastrointestinal toxicity and gastrointestinal intolerability.[11 12] In addition, the health care systems of Western countries are overstretched because of the increasing joint replacement requirements.[13] In this context, identification of the efficacy of existing treatments or development of novel therapies remains an important priority.

Description of the intervention

Acupuncture has long been recognized as a nonpharmacologic therapy in treating various disorders by inserting fine needles into specific anatomic points (acupoints) on the skin of the patient's body. As an important component of traditional Chinese medicine (TCM), acupuncture has been used in clinical practice for more than 3000 years.

The World Health Organization (WHO) has recommended acupuncture therapies for 107 diseases. The efficacy of acupuncture for different kinds of pain diseases has been verified by a great deal of high-quality clinical trials.[14-18] Recently, two individual patient data meta-analyses also reported that acupuncture was effective for the treatment of chronic pain, with treatment effects persisting over time.[19 20] In addition, acupuncture appears to be a safe intervention that has rare adverse effects in the hands of competent practitioners.[21-23]

How the intervention might work

Joint inflammation, such as low-grade inflammatory infiltrates within the synovial lining, is common in KOA.[24] Neurogenic inflammation produced by nociceptors is also found in KOA. Inflammatory mediators in the knee joint can sensitize nociceptors, leading to pain. Furthermore, KOA pain might be caused by other mechanisms, including activation of nociceptive pathways by nerve growth factor (NGF), direct effects of cytokines and chemokines on neurons, or infiltration of the spinal cord by immune cells.[25]

In recent decades, preclinical investigations of acupuncture mechanisms in KOA

pain have increased. These studies show that acupuncture relieves symptoms of KOA by activating a variety of bioactive chemicals through peripheral, spinal, and supraspinal mechanisms. [26] For example, acupuncture can desensitize peripheral nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord. [26-28] In addition, acupuncture dampens the transmission of noxious inputs at the spinal level with the involvement of spinal opioids, serotonin (i.e., 5-hydroxytryptamine), norepinephrine, glial cell/cytokines, and signal molecules.[26 29-31]

Why it is important to perform this review

Research on acupuncture for KOA has been growing, but the findings have been inconsistent. Different guidelines do not reach an agreement on whether acupuncture should be recommended as an effective nonpharmacological treatment for KOA.[8 32-34] In 2004 and 2005, the efficacy of acupuncture for treating KOA was verified by two randomized trials.[14 15] In 2014, however, a clinical trial showed that acupuncture did not confer a benefit over sham treatment for pain or function.[35]

Most meta-analyses mainly focused on chronic pain and peripheral joint osteoarthritis and were not specific to knee osteoarthritis.[19 20 36-39] Although there were some systematic reviews conducted to establish the association of acupuncture with KOA, few drew a definitive conclusion.[40 41] One systematic review have looked at the comparative effectiveness of manual acupuncture and electroacupuncture, but considered only direct evidence.[42] Two previous meta-analyses have drawn opposite conclusions depending on the types of control group used for comparison in 2007.[43 44] However, some rigorous randomized clinical trials (RCTs) in this field published

within recent years were not included in previous systematic reviews. For example, a multicenter RCT published in 2020 by our team suggested that acupuncture had potential benefits for KOA.[45] Thus, it is important to perform a systematic review and meta-analysis to inform clinical practice.

Objectives

We aim to evaluate the efficacy and safety of acupuncture for treating patients with osteoarthritis of the knee by conducting a systematic review and meta-analysis. For this purpose, we put forward the following questions about this review:

1. Is acupuncture effective for treating osteoarthritis of the knee compared with sham control or no-acupuncture control?

2. Is acupuncture associated with a reduction in medication use in patients with KOA?

2. METHODS AND ANALYSIS

Protocol registration.

This protocol was registered in PROSPERO (CRD42021232177). It will be followed the standard methods of systematic review and meta-analysis. It will adher to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) reporting guidelines (see appendix 1).[46 47]

Criteria for including studies in this review

Types of studies

RCTs (with or without blinding, including crossover design) of acupuncture therapy for KOA will be included. We will consider including older RCTs that were cited in previous reviews of acupuncture for osteoarthritis.

Types of participants

Participants with a diagnosis of KOA will be included regardless of their age, sex, race, education or economic status. The diagnosis will be made on the basis of symptoms (pain, brief physical stiffness, and functional limitations) and the radiologic confirmation of osteoarthritis according to the American College of Rheumatology clinical criteria or National Institute for Health and Clinical Excellence guidelines.[8 48]

Types of Interventions

The eligible intervention is acupuncture including manual acupuncture and electroacupuncture. There will be no restriction on the sessions of acupuncture, needling techniques or stimulation methods.

Types of control groups

In this review, we plan to compare needle acupuncture with sham acupuncture, analgesic, usual care or waiting list control groups. Acupuncture plus one or more therapies with the same therapies also will be included.

Outcomes

Primary outcome

Pain intensity: The WOMAC Pain Subscale, Visual Analog Scale (VAS), Brief Pain Inventory (BPI), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) or other validated outcome measures.

Secondary outcomes

1. Function: The WOMAC Function Subscale, Lysholm Scale or other validated scales.

2. Quality of life: The 12-Item Short Form Health Survey (SF-12), 36-Item Short Form Health Survey (SF-36), Assessment of Quality of Life Instrument (AQoL II) or other validated scales.

3. Adverse events: Incidence and severity of adverse events

4. Drug use: Number of people using emergency analgesics, frequency or dosage of medication for KOA.

5. Cost: incremental cost-effectiveness ratio of acupuncture treatment

Criteria for excluding studies in this review

1. Participants with knee pain but no other symptoms of KOA;

2. The intervention group received transcutaneous electrical nerve stimulation;

3. Follow-up periods less than 6 weeks in duration[44];

4. Studies reported only improvement rates;

5. Low quality of internal validity (allocation concealment is determined to be inadequate);

6. Study comparing one type of acupuncture with other type of acupuncture and study comparing acupuncture with complementary therapies or TCM.

Search methods for identification of studies

Electronic searches

We developed search strategies for four English databases (PubMed, Embase, Cochrane Library databases, and Web of Science) and four Chinese databases (China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, and Wanfang) from database inception to

September 1, 2021. Additional trials will be identified by searching previous systematic reviews. No language or publication status restrictions are applied. The search strategy components are clinical condition (osteoarthritis, knee, patellofemoral pain syndrome, knee pain, and gonarthrosis), intervention (acupuncture, electroacupuncture, and acupuncture points) and study type (randomized controlled trial). We will adapt the search strategies to medical subject headings terms and keywords as necessary for each database (see appendix 2 for the search strategy used in the PubMed database). A pilot of the systematic search was conducted on 28 February 2021 (see appendix 3). We (F-TY and C-YL) will rerun the searches before submission of the manuscript to identify any eligible articles published since our first search.

Searching other sources

We will search the following websites as a supplement: the WHO International Clinical Trials Registry Platform and the National Institutes of Health clinical registry ClinicalTrials.gov and the Chinese Clinical Registry. The search will also include a manual search for gray literature (e.g., unpublished conference articles).

Data collection and analysis

Selection of studies

All search results will be exported to EndNote, where we will check for and exclude duplicates. Two of us will screen all titles and abstracts independently to identify potentially relevant studies. Full texts will be downloaded and printed for further assessment. Two reviewers will screen the whole-length articles to confirm whether

the studies meet the inclusion criteria. Any disagreement will be settled by discussion. If an agreement cannot be reached, a third reviewer will be consulted. The reasons for excluding studies will be recorded. The study selection process is shown in figure 1.

Data extraction and management

All data will be extracted independently and in duplicate by two reviewers with a predesigned data extraction template. Disagreements will be settled by discussion. A third reviewer will be consulted if discrepancies cannot be resolved. All data will be cross-checked by two reviewers and transferred into Microsoft Office Excel. If required, we will contact the corresponding authors for more information by email.

The predefined variables for extraction are the following:

1. Publication details (study year, first author, funding source);

2. Basic information (location, study type, number of centers, sample size, study duration, and length of follow-up);

3. Participants (type and/or stage of KOA, mean age, sex, and pain intensity before treatment);

4. Interventions (type of acupuncture, choice of acupuncture points, number of sessions, treatment frequency, duration of each session, and needling techniques)

5. Control (if there is any control, details of the treatment, including the name, dosage, frequency and course);

6. Outcomes (data and time points for each measurement, type and number of adverse events in each group).

Risk of bias assessment in included studies

Two reviewers will assess the risk of bias in the included studies by using the Cochrane Collaboration's tool for assessing risk of bias. We will assess each RCT a low, high, or unclear risk of bias for 6 domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of researchers and participants), attrition bias (incomplete outcome data), ascertainment bias (blinding of outcome assessment), reporting bias (selective outcome reporting) and other sources of potential bias. Disagreements will be resolved by discussion, according to the published articles and supplementary materials. We will consult the third reviewer and contact the study authors when needed.

Acupuncture adequacy assessment

We will try to use some methods to assess treatment adequacy in acupuncture RCTs. We will adopt the adequacy assessment instrument, which was derived from the STRICTA recommendations,[49] to evaluate the following 6 aspects of acupuncture treatment: acupuncture rationale, needling details, treatment regimen, cointerventions, practitioner background, and control intervention(s). We plan to assess adequacy independently and to reach an agreement by discussion. The assessors, who will be blinded to the results of the study and the publication, will conduct the assessments only based on the description of the study population and the acupuncture procedure. To test the success of the blinding, we will ask the two assessors to guess the provenance of each study.

Heterogeneity assessment

If there are sufficient data, we will conduct a meta-analysis to determine the efficacy

of acupuncture and the related factors. I^2 testing will be used to quantify heterogeneity among the included studies.[50] If the I^2 is less than 75%, we will conduct a meta-analysis. We will present summary estimates in forest plots. If the I^2 is more than 50%, we will explore the possible sources of heterogeneity via meta-regression and subgroup analyses. If a meta-analysis is precluded, we will conduct a descriptive synthesis using a best-evidence synthesis approach.

Reporting bias assessment

We will also consider assessing the reporting bias and small-study effects by using funnel plots when there are 10 or more trials. We will assess funnel plot asymmetry by using Begg's and Egger's tests and will define significant publication bias as a p value < 0.1. We will also use a trim-and-fill computation to estimate the effect of publication bias on the interpretation of the results.[51]

DATA SYNTHESIS

When the meta-analysis is performed, Stata 16.0 and RevMan 5.3 will be used for all statistical calculations. The fixed-effects model will be used if little heterogeneity. On the other hand, the random-effects model will be used if significant heterogeneity is observed. For dichotomous variables, Mantel-Haenszel method will be used for analyses and effect size will be reported as relative risk (RR) with 95% confidence intervals (CIs). For continuous variables, inverse variance method will be used for analyses and treatment effect will be reported as mean difference (MD) with 95% CIs. The standardized mean difference (SMD) with 95% CIs will be used if different scales are used to evaluate a predesigned outcome.

For pain variance, we plan to pool data from previous studies reporting VAS 100 mm, VAS 10 cm, and NRS by transforming it to a "0-100-pain measure" using an appropriate multiplier. We also intend to analyze pain intensity by independently reporting the aforementioned scales.

SUBGROUP ANALYSIS

Subgroup analyses will be performed to explain the heterogeneity. Predefined subgroups include the type of intervention, the frequency of acupuncture treatment, and the stage of knee osteoarthritis.

SENSITIVITY ANALYSIS

We will conduct a sensitivity analysis to verify the robustness of the review conclusions. We will consider removing one study at a time to observe its effect on heterogeneity and effect size. In addition, the meta-analysis will be repeated after low-quality studies are excluded.

Strength of recommendations and the quality of evidence

We will assess the strength of recommendations based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) working group methodology. The two categories of weak/conditional evidence and strong evidence will be used.

We will also assess the quality of evidence. The quality of evidence will be assessed according to the domains of risk of bias, consistency, directness, precision, and publication bias. The assessments will be adjudicated into four levels: high, moderate, low or very low.[52 53]

Patients and public involvement

There were no patients nor public will be directly involved in this review. Only data already existent in the literature and the aforementioned sources will be used for this study.

DISCUSSION

This systematic review will be performed based on previous studies of acupuncture for knee osteoarthritis. Conclusions drawn from this review may be beneficial to patients with KOA, clinicians and policy makers. We will summarize and explain the characteristics and findings of the included studies by conducting a systematic narrative synthesis.

Based on the above, we want to conduct some exploratory studies. (1) Is there a difference in the efficacy between manual acupuncture and electroacupuncture? (2) Is the efficacy (if any) related to the stage of knee osteoarthritis according to the Kellgren-Lawrence score or Outbridge score,[54 55] some characteristics of acupuncture (e.g., choice of acupoints and treatment frequency), type of control group, measurement time points of outcomes or other variables?

Manual acupuncture and electroacupuncture are the most commonly used acupuncture therapies. Manual acupuncture maintains a moderate dose of stimulation by lifting, inserting and twisting needles to acupoints. However, it is laborious and difficult to reach an agreement on standards because of the different needle techniques. Electroacupuncture, which is widely used in clinical practice, refers to the pulse current input to acupoints on the basis of needle acupuncture. This approach can

accurately control the dose of stimulation and save labor. In clinical trials for pain conditions, better analgesia appears to be obtained when electrical stimulation is added to manual stimulation than with manual acupuncture needle stimulation alone.[56] However, the findings may not be generalizable because of the different pain types. We will try to explore the difference in the efficacy between manual acupuncture and electroacupuncture for KOA. Hence, we will choose sham acupuncture as a common comparator, making an indirect comparison between manual acupuncture and electroacupuncture. Finally, we will conduct a mixed treatment comparison meta-analysis (MTC) to synthesize the evidence from direct comparison and indirect comparison.

There are many factors affecting the efficacy of acupuncture. Our previous studies suggested that the effect of acupuncture may be associated with the dose of acupuncture, including needled points, Deqi response, frequency of treatment and number of treatment sessions.[57 58] Hence, we want to focus on these factors in the subgroup analysis and to explore the applied law of different doses of acupuncture.

We predefine that trials included have 6 weeks of observation at least. Although this criterion has not been accepted widely, we think that RCTs with observation periods less than 6 weeks may have methodological shortcomings that may exaggerate the efficacy of acupuncture.

The proposed review has several strengths. We plan to search multiple Chinese and English language databases to ensure a comprehensive search of the literature. Any meta-analyses will be performed according to the Cochrane Handbook for Systematic

Reviews of Interventions. A further strength is that more stringent eligibility criteria will be applied to ensure the quality of the included RCTs. In addition, pain intensity was selected as the targeted outcome because it plays an important role in the pain management of KOA. Transformation of pain scores measured by different pain scales to a 0-100 pain measure will result in loss of some accuracy; however, we believe that it is clinically irrelevant.

Contributors C-YL is the guarantor and first author of the protocol. C-YL and L-QW designed the systematic review. C-YL and L-LL drafted the manuscript. J-WY, J-FT, L-QW and Myeong Soo Lee provided help to design and edited the manuscript. C-YL and F-TY will independently screen the eligible studies. C-YL and X-WH will extract data from included articles. J-LL and J-FT will assess the risk of bias. C-YL and X-TS will assess acupuncture adequacy, Strength of recommendations and the quality of evidence. C-YL, L-YQ and S-YY will finish data synthesis. L-QW will arbitrate any disagreements during the review. All authors have read the manuscript and approved the final publication of the protocol.

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Figure legends

Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

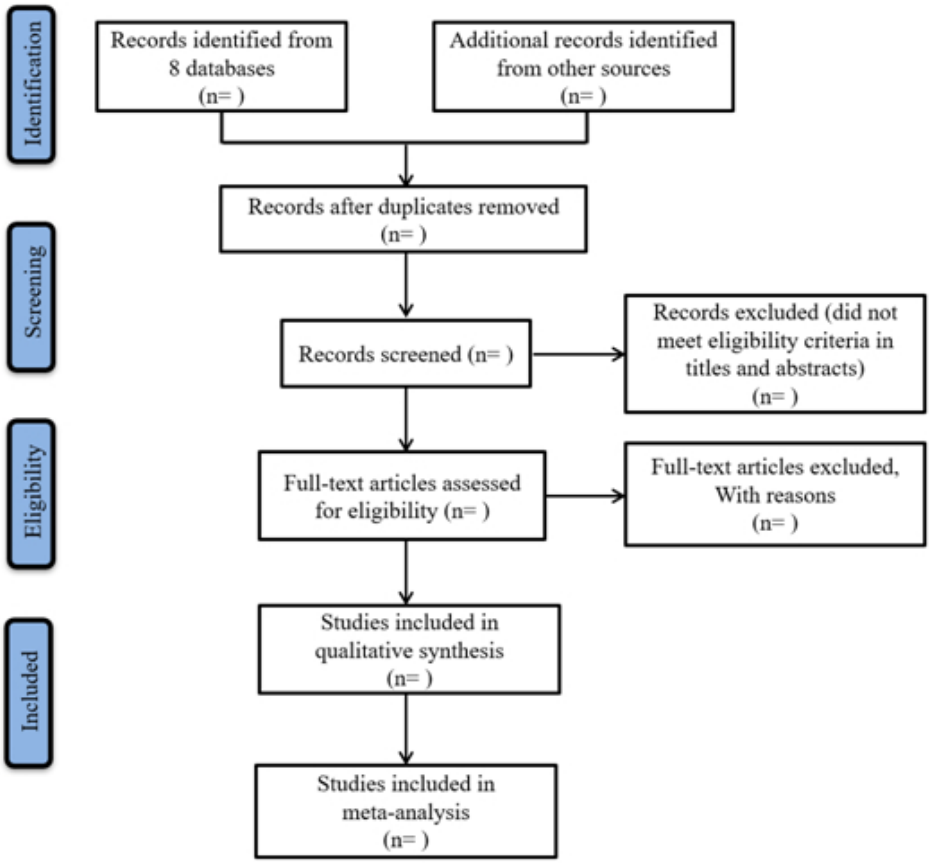

Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

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

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	18
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	18
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-10
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	10-11
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	10-11 Appendix2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12

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)	11-12
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	12
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	N/A
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10;18
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 I^2, Kendall's τ)	14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

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

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

Table 1 Search strategy used in the PubMed database

#	**Searches**
1	Osteoarthritis, Knee[mesh]
2	Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract]
3	Patellofemoral Pain Syndrome[mesh]
4	Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract]
5	knee pain[Title/Abstract]
6	gonarthrosis[Title/Abstract]
7	OR/1-6
8	Acupuncture[mesh]
9	Pharmacopuncture[Title/Abstract]
10	Acupuncture Therapy[mesh]
11	Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract]
12	Electroacupuncture[mesh]
13	Acupuncture Points[mesh]
14	Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract]
15	OR/8-14
16	clinical[tiab]
17	trial[tiab]
18	16 AND 17
19	clinical trials as topic[mesh]
20	clinical trial[pt]
21	random*[tiab]
22	random allocation[mesh]
23	therapeutic use[sh]
24	OR/18-23
25	7 AND 15 AND 24

Result of presearch in the PubMed database

1. Osteoarthritis, Knee[mesh] Items found: 21,147
2. Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract] Items found: 40,291
3. Patellofemoral Pain Syndrome[mesh] Items found: 934
4. Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract] Items found: 3,799
5. knee pain[Title/Abstract] Items found: 8,083
6. gonarthrosis[Title/Abstract] Items found: 1,095
7. OR/1-6 Items found: 47,408
8. Acupuncture[mesh] Items found: 1735
9. Pharmacopuncture[Title/Abstract] Items found: 211
10. Acupuncture Therapy[mesh] Items found: 25,321
11. Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract] Items found: 2996
12. Electroacupuncture[mesh] Items found: 4128
13. Acupuncture Points[mesh] Items found: 6934
14. Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract] Items found: 6,284
15. OR/8-14 Items found: 27,954
16. clinical[tiab] Items found: 3,720,276
17. trial[tiab] Items found: 638,665
18. 16 AND 17 Items found: 294,477
19. clinical trials as topic[mesh] Items found: 353,132
20. clinical trial[pt] Items found: 884,322
21. random*[tiab] Items found: 1,202,203
22. random allocation[mesh] Items found: 104,737
23. therapeutic use[sh] Items found: 4,516,532
24. OR/18-23 Items found: 5,668,908
25. 7 AND 15 AND 24 Items found: 397

Final Result: 397 (By 28 February 2021)

BMJ Open

Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, COMPLEMENTARY MEDICINE

Title: Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

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Key words: Acupuncture; Osteoarthritis, Knee; Meta-Analysis; Protocol

Number of words: 3525

ABSTRACT

Introduction

Knee osteoarthritis is one of the leading causes of disability. The effectiveness of acupuncture for treating KOA remains controversial. This protocol describes the method of a systematic review and meta-analysis evaluating the efficacy and safety of acupuncture for treating KOA.

Methods and analysis

Four English databases (PubMed, Embase, Cochrane Library databases, and Web of Science) and four Chinese databases (China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, and Wanfang) will be searched from the database inception to September 1, 2021. All randomized controlled trials related to acupuncture for KOA will be included. Extracted data will include publication details, basic information, demographic data, intervention details and patient outcomes. The primary outcome is pain intensity. Risk of bias will be assessed using the Cochrane Collaboration's tool for assessing risk of bias. Article selection, data extraction and risk of bias assessment will be performed in duplicate by two independent reviewers. If the meta-analysis is precluded, we will conduct a descriptive synthesis using a best-evidence synthesis approach. The strength of recommendations and quality of evidence will be assessed using the Grading of Recommendations Assessment Development and Evaluation working group methodology.

Ethics and dissemination

Ethics approval is not required because individual patient data are not included. This protocol was registered in the international Prospective Register of Systematic Reviews on 25 February 2021. The systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal. The findings will also be disseminated through conference presentations.

Trial registration number

CRD42021232177

Article summary

Strengths and limitations of this study

1. This meta-analysis will evaluate the effectiveness and safety of acupuncture in treating knee osteoarthritis by collecting comprehensive evidence.
2. We want to focus on many different factors in subgroup analysis and to explore the applied law of different doses of acupuncture.
3. This study will explore the difference in the effectiveness between manual acupuncture and electroacupuncture for knee osteoarthritis by synthesizing the evidence from direct comparison and indirect comparison.
4. We plan to search multiple Chinese and English language databases to ensure a comprehensive search of the literature.
5. Transformation of pain scores will result in loss of some accuracy; however, we believe that it is clinically irrelevant.

INTRODUCTION

Description of the condition

Osteoarthritis (OA) is a common clinical degenerative disease and is one of the leading causes of disability.[1] The excess costs of adults with OA are considerable, estimated at $45 billion annually in United States.[2] Knee osteoarthritis accounts for approximately 85% of global osteoarthritis burden.[3] With the trends of an aging population and increasing obesity, the incidence of knee osteoarthritis (KOA) is increasing for both sexes.[4 5] In addition, pain symptoms associated with KOA result in physical and walking disability, which in turn have an excess risk of all-cause mortality. [6 7]

Exercise and weight loss, two effective nonpharmacological treatments, are strongly recommended in all people with clinical osteoarthritis.[8] However, for patients with KOA, it is difficult to continue exercising and losing weight. Representatives of pharmacological interventions include analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). However, acetaminophen (paracetamol) is not associated with long-term pain improvement.[9] Furthermore, many NSAIDs are associated with serious side effects such as cardiovascular, renal adverse effects and gastrointestinal bleeding.[10 11] In addition, the health care systems of Western countries are overstretched because of the increasing joint replacement requirements.[12] In this context, identification of the efficacy of existing treatments or development of novel therapies remains an important priority.

Description of the intervention

Acupuncture has long been recognized as a nonpharmacologic therapy in treating various disorders by inserting fine needles into specific anatomic points (acupoints) on the skin of the patient's body. As an important component of traditional Chinese medicine (TCM), acupuncture has been used in clinical practice for more than 3000 years.

The World Health Organization (WHO) has recommended acupuncture therapies for 107 diseases. The efficacy of acupuncture for different kinds of pain diseases has been verified by a great deal of high-quality clinical trials.[13-15] Recently, two individual patient data meta-analyses also reported that acupuncture was effective for the treatment of chronic pain, with treatment effects persisting over time.[16 17] In addition, acupuncture appears to be a safe intervention that has rare adverse effects in the hands of competent practitioners.[18 19]

How the intervention might work

Knee osteoarthritis (KOA) is a prevalent, chronic joint disorder, characterized by synovitis, overgrowth of subchondral bone, development of osteophytes, erosions and loss of the articular cartilage. Previous study found that cartilage damage is the origin and result of KOA. With the further study of KOA, synovitis has been verified to play a crucial part in the pathological development and the maintenance of pain in KOA.[20]

In recent decades, preclinical investigations of acupuncture mechanisms in KOA pain have increased. These studies show that acupuncture relieves symptoms of KOA by activating a variety of bioactive chemicals through peripheral, spinal, and supraspinal mechanisms.[21] For example, acupuncture can desensitize peripheral

nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord.[21-23] In addition, acupuncture dampens the transmission of noxious inputs at the spinal level with the involvement of spinal opioids, serotonin (i.e., 5-hydroxytryptamine), norepinephrine, glial cell/cytokines, and signal molecules.[21 24-26] In addition, CBR1-GABA-5-HT may be a novel pathway contributed to the effect of EA on KOA pain.[27] EA down-regulated IL-1β expression via activating the peripheral CBR2 to inhibit the KOA pain.[28]

Why it is important to perform this review

Research on acupuncture for KOA has been growing, but the findings have been inconsistent. Different guidelines do not reach an agreement on whether acupuncture should be recommended as an effective nonpharmacological treatment for KOA.[8 29-31] In 2014, a clinical trial showed that acupuncture did not confer a benefit over sham treatment for pain or function.[32] In 2019, however, a review suggested that acupuncture provided relief of pain associated with KOA.[33]

Most meta-analyses mainly focused on chronic pain and peripheral joint osteoarthritis and were not specific to knee osteoarthritis.[16 17 34-37] Although there were some systematic reviews conducted to establish the association of acupuncture with KOA, few drew a definitive conclusion.[38 39] One systematic review has looked at the comparative effectiveness of manual acupuncture (MA) and electroacupuncture (EA), but considered only direct evidence.[40] Two previous meta-analyses have drawn opposite conclusions depending on the types of control group used for comparison in 2007.[41 42] However, some rigorous randomized clinical trials (RCTs) in this field

published within recent years were not included in previous systematic reviews. For example, a multicenter RCT published in 2020 by our team suggested that acupuncture had potential benefits for KOA.[43] Thus, it is important to perform a systematic review and meta-analysis to inform clinical practice.

Objectives

We aim to evaluate the efficacy and safety of acupuncture for treating patients with osteoarthritis of the knee by conducting a systematic review and meta-analysis. For this purpose, we put forward the following questions about this review:

1. Is acupuncture effective for treating osteoarthritis of the knee compared with sham control or no-acupuncture control?

2. Is there a difference in the effectiveness between manual acupuncture and electroacupuncture?

2. METHODS AND ANALYSIS

Patients and public involvement

There will be no patients or public directly involved in this review. Only data already existent in the literature and the aforementioned sources will be used for this study.

Protocol registration.

This protocol was registered in PROSPERO (CRD42021232177). It will be followed the standard methods of systematic review and meta-analysis. It will adher to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) reporting guidelines (see appendix 1).[44 45]

Criteria for including studies in this review

Types of studies

RCTs (with or without blinding, including crossover design) of acupuncture therapy for KOA will be included. We will consider including older RCTs that were cited in previous reviews of acupuncture for osteoarthritis.

Types of participants

Studies enrolling participants diagnosed as KOA will be included. The diagnostic criteria should be based on the American College of Rheumatology clinical criteria, National Institute for Health and Clinical Excellence guidelines or any other accepted guidelines.[8 46]There will be no restrictions on their age, sex, race, education, economic status, Kellgren-Lawrence score or Outbridge score.[47 48]

Types of Interventions

The eligible intervention is acupuncture including manual acupuncture and electroacupuncture. There will be no restriction on the sessions of acupuncture, needling techniques or stimulation methods.

Types of control groups

In this review, we plan to compare needle acupuncture with sham acupuncture, analgesic, usual care or waiting list control groups. Acupuncture plus one or more therapies with the same therapies also will be included.

Outcomes

Primary outcome

Pain intensity: The WOMAC Pain Subscale, Visual Analog Scale (VAS), Brief Pain Inventory (BPI), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) or other

validated outcome measures.

Secondary outcomes

1. Function: The WOMAC Function Subscale, Lysholm Scale or other validated scales.

2. Quality of life: The 12-Item Short Form Health Survey (SF-12), 36-Item Short Form Health Survey (SF-36), Assessment of Quality of Life Instrument (AQoL II) or other validated scales.

3. Adverse events: Incidence and severity of adverse events

4. Drug use: Number of people using emergency analgesics, frequency or dosage of medication for KOA.

5. Cost: incremental cost-effectiveness ratio of acupuncture treatment

Criteria for excluding studies in this review

1. Participants with knee pain but no other criteria of KOA;

2. The intervention group received transcutaneous electrical nerve stimulation;

3. Studies reported only improvement rates;

4. Studies comparing one type of acupuncture with other type of acupuncture (except EA versus MA) and studies comparing acupuncture with complementary therapies or TCM.

Search methods for identification of studies

Electronic searches

We developed search strategies for four English databases (PubMed, Embase, Cochrane Library databases, and Web of Science) and four Chinese databases (China

National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, and Wanfang) from database inception to September 1, 2021. Additional trials will be identified by searching previous systematic reviews. No language or publication status restrictions are applied. The search strategy components are clinical condition (osteoarthritis, chondromalacia patellae, knee, knee pain, and gonarthrosis), intervention (acupuncture, electroacupuncture, and acupuncture points) and study type (randomized controlled trial). We will adapt the search strategies to medical subject headings terms and keywords as necessary for each database (see appendix 2 for the search strategy used in the PubMed database). A pilot of the systematic search was conducted on 28 February 2021 (see appendix 3). We (F-TY and C-YL) will rerun the searches before submission of the manuscript to identify any eligible articles published since our first search.

Searching other sources

We will search the following websites as a supplement: the WHO International Clinical Trials Registry Platform and the National Institutes of Health clinical registry ClinicalTrials.gov and the Chinese Clinical Registry. The search will also include a manual search for gray literature (e.g., unpublished conference articles).

Data collection and analysis

Selection of studies

All search results will be exported to EndNote, where we will check for and exclude duplicates. Two of us will screen all titles and abstracts independently to identify

potentially relevant studies. Full texts will be downloaded and printed for further assessment. Two reviewers will screen the whole-length articles to confirm whether the studies meet the inclusion criteria. Any disagreement will be settled by discussion. If an agreement cannot be reached, a third reviewer will be consulted. The reasons for excluding studies will be recorded. The study selection process is shown in figure 1. Besides, we will add a table of exclude studies with reasons for exclusion to the appendix of our meta-analysis.

Data extraction and management

All data will be extracted independently and in duplicate by two reviewers with a predesigned data extraction template. Disagreements will be settled by discussion. A third reviewer will be consulted if discrepancies cannot be resolved. All data will be cross-checked by two reviewers and transferred into Microsoft Office Excel. If required, we will contact the corresponding authors for more information by email.

The predefined variables for extraction are the following:

1. Publication details (study year, first author, funding source);

2. Basic information (location, study type, number of centers, sample size, study duration, and length of follow-up);

3. Participants (type and/or stage of KOA, mean age, sex, and pain intensity before treatment);

4. Interventions (type of acupuncture, choice of acupuncture points, number of sessions, treatment frequency, duration of each session, and needling techniques)

5. Control (if there is any control, details of the treatment, including the name, dosage,

frequency and course);

6. Outcomes (data and time points for each measurement, type and number of adverse events in each group).

Risk of bias assessment in included studies

Two reviewers will assess the risk of bias in the included studies by using the Cochrane Collaboration's tool for assessing risk of bias. We will assess each RCT a low, high, or unclear risk of bias for 6 domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of researchers and participants), attrition bias (incomplete outcome data), ascertainment bias (blinding of outcome assessment), reporting bias (selective outcome reporting) and other sources of potential bias. Disagreements will be resolved by discussion, according to the published articles and supplementary materials. We will consult the third reviewer and contact the study authors when needed.

Acupuncture adequacy assessment

We will use the adequacy assessment instrument to assess treatment adequacy in acupuncture RCTs from the following 4 aspects of acupuncture treatment: choice of acupuncture points, number of sessions, needling technique, and experience of the acupuncturists[42]. Two assessors who are experienced acupuncturists will assess adequacy independently and reach an agreement by discussion. They will be blinded to the results of the study and the publication and conduct the assessments only based on the description of the study population and the acupuncture procedure. To test the success of the blinding, we will ask the assessors to guess the provenance of each

study.

Heterogeneity assessment

If there are sufficient data, we will conduct a meta-analysis to determine the efficacy of acupuncture and the related factors. I^2 testing will be used to quantify heterogeneity among the included studies.[49] We will present summary estimates in forest plots. If the I^2 is more than 50%, we will explore the possible sources of heterogeneity via meta-regression and subgroup analyses. If a meta-analysis is not appropriate, we will conduct a descriptive synthesis using a best-evidence synthesis approach.

Reporting bias assessment

We will also consider assessing the reporting bias and small-study effects by using funnel plots when there are 10 or more trials. We will assess funnel plot asymmetry by using Begg's and Egger's tests and will define significant publication bias as a p value < 0.1. We will also use a trim-and-fill computation to estimate the effect of publication bias on the interpretation of the results.[50]

DATA SYNTHESIS

When the meta-analysis is performed, Stata 16.0 and RevMan 5.3 will be used for all statistical calculations. All the analyses will be based on the random-effects model because the RCTs included by us came from different populations. For dichotomous variables, Mantel-Haenszel method will be used for analyses and effect size will be reported as relative risk (RR) with 95% confidence intervals (CIs). For continuous variables, inverse variance method will be used for analyses and treatment effect will be reported as mean difference (MD) with 95% CIs. The standardized mean

difference (SMD) with 95% CIs will be used if different scales are used to evaluate a predesigned outcome.

For pain variance, we plan to pool data from previous studies reporting VAS 100 mm, VAS 10 cm, and NRS by transforming it to a "0-100-pain measure" using an appropriate multiplier. We also intend to analyze pain intensity by independently reporting the aforementioned scales.

SUBGROUP ANALYSIS

Subgroup analyses will be performed to explain the heterogeneity. Predefined subgroups include the location of studies, the type of intervention, the dosage of acupuncture, and the stage of knee osteoarthritis.

SENSITIVITY ANALYSIS

We will conduct a sensitivity analysis to verify the robustness of the review conclusions. We will consider removing one study at a time to observe its effect on heterogeneity and effect size. In addition, the meta-analysis will be repeated after studies with lack of allocation concealment are excluded.

OTHER ANALYSIS

If manual acupuncture and eletroacupuncture are effective for KOA compared with sham acupuncture, we will conduct the exploratory research to compare the difference in the effectiveness between MA and EA by synthesizing the evidence from direct comparison and indirect comparison. For direct comparison results, we will use Revman to analyze. For the indirect comparison, we will choose sham acupuncture as a common comparator and use R software to analyze. Finally, we will conduct a

mixed treatment comparison meta-analysis (MTC) to synthesize the evidence from direct comparison and indirect comparison.

Strength of recommendations and the quality of evidence

We will assess the strength of recommendations based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) working group methodology. The two categories of weak/conditional evidence and strong evidence will be used.

We will also assess the quality of evidence. The quality of evidence will be assessed according to the domains of risk of bias, consistency, directness, precision, and publication bias. The assessments will be adjudicated into four levels: high, moderate, low or very low.[51 52]

DISCUSSION

This systematic review will be performed based on previous studies of acupuncture for knee osteoarthritis. Conclusions drawn from this review may be beneficial to patients with KOA, clinicians and policy makers. We will summarize and explain the characteristics and findings of the included studies by conducting a systematic narrative synthesis.

Based on the above, we want to conduct some exploratory studies. (1) Is there a difference in the effectiveness between manual acupuncture and electroacupuncture? (2) Is the efficacy (if any) related to the stage of knee osteoarthritis according to the Kellgren-Lawrence score or Outbridge score, some characteristics of acupuncture (e.g., treatment frequency), type of control group, measurement time points of

outcomes or other variables?

Manual acupuncture and electroacupuncture are the most commonly used acupuncture therapies. Manual acupuncture maintains a moderate dose of stimulation by lifting, inserting and twisting needles to acupoints. However, it is laborious and difficult to reach an agreement on standards because of the different needle techniques. Electroacupuncture, which is widely used in clinical practice, refers to the pulse current input to acupoints on the basis of needle acupuncture. This approach can accurately control the dose of stimulation and save labor. In clinical trials for pain conditions, better analgesia appears to be obtained when electrical stimulation is added to manual stimulation than with manual acupuncture needle stimulation alone.[53] However, the findings may not be generalizable because of the different pain types.

There are many factors affecting the efficacy of acupuncture. One review presented "the challenge of adequacy of dose" recently.[33] Our group built a scoring instrument to calculate the dose of acupuncture from four parameters.[54] Based on the sum of the scores, we defined three doses of acupuncture treatment: high dosage, medium dosage and low dosage. And we designed three subgroups according the three kinds of dosage to explore the relationship between doses of acupuncture and efficacy. Deqi response is a comprehensive sensation of soreness, numbness, heaviness, aching at and around acupoints produced by manipulation of the needles. It plays a role in acupuncture dosage so it is only one dimension of our scoring instrument.

The proposed review has several strengths. We plan to search multiple Chinese and

English language databases to ensure a comprehensive search of the literature. Any meta-analyses will be performed according to the Cochrane Handbook for Systematic Reviews of Interventions. A further strength is that stringent eligibility criteria will be applied to ensure the quality of the included RCTs. In addition, pain intensity was selected as the targeted outcome because it plays an important role in the pain management of KOA. Transformation of pain scores measured by different pain scales to a 0-100 pain measure will result in loss of some accuracy; however, we believe that it is clinically irrelevant.

Ethics and dissemination

Ethics approval is not required because individual patient data are not included. This protocol was registered in the international Prospective Register of Systematic Reviews on 25 February 2021. The systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal. The findings will also be disseminated through conference presentations.

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Contributors C-YL is the guarantor and first author of the protocol. C-YL and L-QW designed the systematic review. C-YL and L-LL drafted the manuscript. J-WY, J-FT, L-QW and Myeong Soo Lee provided help to design and edited the manuscript. C-YL and F-TY will independently screen the eligible studies. C-YL and X-WH will extract data from included articles. J-LL and J-FT will assess the risk of bias. C-YL and X-TS will assess acupuncture adequacy, Strength of recommendations and the quality

of evidence. C-YL, L-YQ and S-YY will finish data synthesis. L-QW will arbitrate any disagreements during the review. All authors have read the manuscript and approved the final publication of the protocol.

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Figure legends

Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

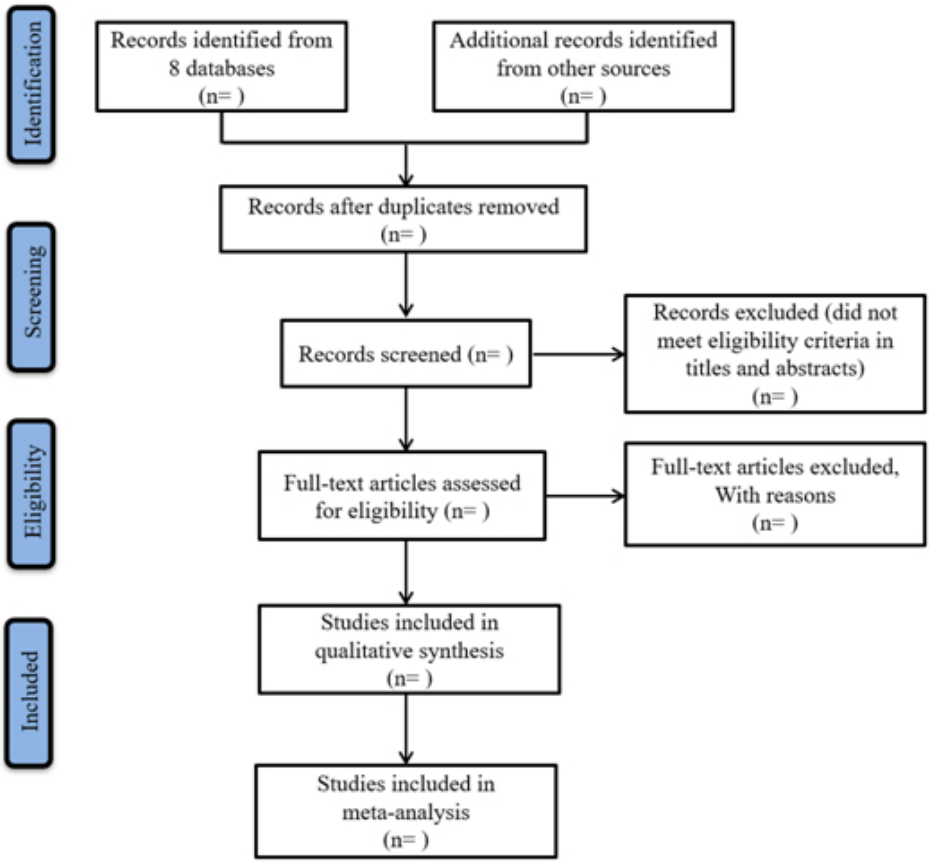

Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

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

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18-19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
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
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
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	10-11
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	10-11 Appendix2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12

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)	11-12
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	12
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	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
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 I^2, Kendall's τ)	14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

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

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

Table 1 Search strategy used in the PubMed database

#	Searches
1	Osteoarthritis, Knee[mesh]
2	Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract]
3	Patellofemoral Pain Syndrome[mesh]
4	Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract]
5	knee pain[Title/Abstract]
6	gonarthrosis[Title/Abstract]
7	OR/1-6
8	Acupuncture[mesh]
9	Pharmacopuncture[Title/Abstract]
10	Acupuncture Therapy[mesh]
11	Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract]
12	Electroacupuncture[mesh]
13	Acupuncture Points[mesh]
14	Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract]
15	OR/8-14
16	clinical[tiab]
17	trial[tiab]
18	16 AND 17
19	clinical trials as topic[mesh]
20	clinical trial[pt]
21	random*[tiab]
22	random allocation[mesh]
23	therapeutic use[sh]
24	OR/18-23
25	7 AND 15 AND 24

Result of presearch in the PubMed database

1. Osteoarthritis, Knee[mesh] Items found: 21,147
2. Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract] Items found: 40,291
3. Patellofemoral Pain Syndrome[mesh] Items found: 934
4. Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract] Items found: 3,799
5. knee pain[Title/Abstract] Items found: 8,083
6. gonarthrosis[Title/Abstract] Items found: 1,095
7. OR/1-6 Items found: 47,408
8. Acupuncture[mesh] Items found: 1735
9. Pharmacopuncture[Title/Abstract] Items found: 211
10. Acupuncture Therapy[mesh] Items found: 25,321
11. Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract] Items found: 2996
12. Electroacupuncture[mesh] Items found: 4128
13. Acupuncture Points[mesh] Items found: 6934
14. Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract] Items found: 6,284
15. OR/8-14 Items found: 27,954
16. clinical[tiab] Items found: 3,720,276
17. trial[tiab] Items found: 638,665
18. 16 AND 17 Items found: 294,477
19. clinical trials as topic[mesh] Items found: 353,132
20. clinical trial[pt] Items found: 884,322
21. random*[tiab] Items found: 1,202,203
22. random allocation[mesh] Items found: 104,737
23. therapeutic use[sh] Items found: 4,516,532
24. OR/18-23 Items found: 5,668,908
25. 7 AND 15 AND 24 Items found: 397

Final Result: 397 (By 28 February 2021)

BMJ Open

Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
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Complete List of Authors:	Liu, Chuanyang; Beijing University of Chinese Medicine, School of Traditional Chinese Medicine Tu, Jian Feng; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Lee, Myeong Soo; Korea Institute of Oriental Medicine, Medical Research Division Qi, Lingyu; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Yu, Fang-Ting; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina YAN, Shiyan; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Li, Jin-Ling; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Lin, Lu; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Hao, Xiao-Wan; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Su, Xin-Tong; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Yang, Jing-Wen; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Wang, Li-Qiong; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, COMPLEMENTARY MEDICINE

Title: Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

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Key words: Acupuncture; Osteoarthritis, Knee; Meta-Analysis; Protocol

ABSTRACT

Introduction

Knee osteoarthritis is one of the leading causes of disability. The effectiveness of acupuncture for treating KOA remains controversial. This protocol describes the method of a systematic review and meta-analysis evaluating the efficacy and safety of acupuncture for treating KOA.

Methods and analysis

Four English databases (PubMed, Embase, Cochrane Library databases, and Web of Science) and four Chinese databases (China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, and Wanfang) will be searched from the database inception to September 1, 2021. All randomized controlled trials related to acupuncture for KOA will be included. Extracted data will include publication details, basic information, demographic data, intervention details and patient outcomes. The primary outcome is pain intensity. Risk of bias will be assessed using the Cochrane Collaboration's tool for assessing risk of bias. Article selection, data extraction and risk of bias assessment will be performed in duplicate by two independent reviewers. If the meta-analysis is precluded, we will conduct a descriptive synthesis using a best-evidence synthesis approach. The strength of recommendations and quality of evidence will be assessed using the Grading of Recommendations Assessment Development and Evaluation working group methodology.

Ethics and dissemination

Ethics approval is not required because individual patient data are not included. This protocol was registered in the international Prospective Register of Systematic Reviews on 25 February 2021. The systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal. The findings will also be disseminated through conference presentations.

Trial registration number

CRD42021232177

Article summary

Strengths and limitations of this study

1. This meta-analysis will evaluate the effectiveness and safety of acupuncture in treating knee osteoarthritis by collecting comprehensive evidence.
2. We want to focus on many different factors in subgroup analysis and to explore the applied law of different doses of acupuncture.
3. This study will explore the difference in the effectiveness between manual acupuncture and electroacupuncture for knee osteoarthritis by synthesizing the evidence from direct comparison and indirect comparison.
4. We plan to search multiple Chinese and English language databases to ensure a comprehensive search of the literature.
5. Transformation of pain scores will result in loss of some accuracy; however, we believe that it is clinically irrelevant.

INTRODUCTION

Description of the condition

Osteoarthritis (OA) is a common clinical degenerative disease and is one of the leading causes of disability.[1] The excess costs of adults with OA are considerable, estimated at $45 billion annually in United States.[2] Knee osteoarthritis accounts for approximately 85% of global osteoarthritis burden.[3] With the trends of an aging population and increasing obesity, the incidence of knee osteoarthritis (KOA) is increasing for both sexes.[4 5] In addition, pain symptoms associated with KOA result in physical and walking disability, which in turn have an excess risk of all-cause mortality. [6 7]

Exercise and weight loss, two effective nonpharmacological treatments, are strongly recommended in all people with clinical osteoarthritis.[8] However, for patients with KOA, it is difficult to continue exercising and losing weight. Representatives of pharmacological interventions include analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). However, acetaminophen (paracetamol) is not associated with long-term pain improvement.[9] Furthermore, many NSAIDs are associated with serious side effects such as cardiovascular, renal adverse effects and gastrointestinal bleeding.[10 11] In addition, the health care systems of Western countries are overstretched because of the increasing joint replacement requirements.[12] In this context, identification of the efficacy of existing treatments or development of novel therapies remains an important priority.

Description of the intervention

Acupuncture has long been recognized as a nonpharmacologic therapy in treating various disorders by inserting fine needles into specific anatomic points (acupoints) on the skin of the patient's body. As an important component of traditional Chinese medicine (TCM), acupuncture has been used in clinical practice for more than 3000 years.

The World Health Organization (WHO) has recommended acupuncture therapies for 107 diseases. The efficacy of acupuncture for different kinds of pain diseases has been verified by a great deal of high-quality clinical trials.[13-15] Recently, two individual patient data meta-analyses also reported that acupuncture was effective for the treatment of chronic pain, with treatment effects persisting over time.[16 17] In addition, acupuncture appears to be a safe intervention that has rare adverse effects in the hands of competent practitioners.[18 19]

How the intervention might work

Knee osteoarthritis (KOA) is a prevalent, chronic joint disorder, characterized by synovitis, overgrowth of subchondral bone, development of osteophytes, erosions and loss of the articular cartilage. Previous study found that cartilage damage is the origin and result of KOA. With the further study of KOA, synovitis has been verified to play a crucial part in the pathological development and the maintenance of pain in KOA.[20]

In recent decades, preclinical investigations of acupuncture mechanisms in KOA pain have increased. These studies show that acupuncture relieves symptoms of KOA by activating a variety of bioactive chemicals through peripheral, spinal, and supraspinal mechanisms.[21] For example, acupuncture can desensitize peripheral

nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord.[21-23] In addition, acupuncture dampens the transmission of noxious inputs at the spinal level with the involvement of spinal opioids, serotonin (i.e., 5-hydroxytryptamine), norepinephrine, glial cell/cytokines, and signal molecules.[21 24-26] In addition, CBR1-GABA-5-HT may be a novel pathway contributed to the effect of EA on KOA pain.[27] EA down-regulated IL-1β expression via activating the peripheral CBR2 to inhibit the KOA pain.[28]

Why it is important to perform this review

Research on acupuncture for KOA has been growing, but the findings have been inconsistent. Different guidelines do not reach an agreement on whether acupuncture should be recommended as an effective nonpharmacological treatment for KOA.[8 29-31] In 2014, a clinical trial showed that acupuncture did not confer a benefit over sham treatment for pain or function.[32] In 2019, however, a review suggested that acupuncture provided relief of pain associated with KOA.[33]

Most meta-analyses mainly focused on chronic pain and peripheral joint osteoarthritis and were not specific to knee osteoarthritis.[16 17 34-37] Although there were some systematic reviews conducted to establish the association of acupuncture with KOA, few drew a definitive conclusion.[38 39] One systematic review has looked at the comparative effectiveness of manual acupuncture (MA) and electroacupuncture (EA), but considered only direct evidence.[40] Furthermore, some rigorous randomized clinical trials (RCTs) in this field published within recent years were not included in previous systematic reviews. For example, a multicenter RCT published in 2020 by

our team suggested that acupuncture had potential benefits for KOA.[41] Thus, it is important to perform a systematic review and meta-analysis to inform clinical practice.

Objectives

We aim to evaluate the efficacy and safety of acupuncture for treating patients with osteoarthritis of the knee by conducting a systematic review and meta-analysis. For this purpose, we put forward the following questions about this review:

1. Is acupuncture effective for treating osteoarthritis of the knee compared with sham control or no-acupuncture control?

2. Is there a difference in the effectiveness between manual acupuncture and electroacupuncture?

2. METHODS AND ANALYSIS

Patients and public involvement

There will be no patients or public directly involved in this review. Only data already existent in the literature and the aforementioned sources will be used for this study.

Protocol registration.

This protocol was registered in PROSPERO (CRD42021232177). It will be followed the standard methods of systematic review and meta-analysis. It will adher to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) reporting guidelines (see appendix 1).[42 43]

Criteria for including studies in this review

Types of studies

RCTs (with or without blinding, including crossover design) of acupuncture therapy for KOA will be included. We will consider including older RCTs that were cited in previous reviews of acupuncture for osteoarthritis.

Types of participants

Studies enrolling participants diagnosed as KOA will be included. The diagnostic criteria should be based on the American College of Rheumatology clinical criteria, National Institute for Health and Clinical Excellence guidelines or any other accepted guidelines.[8 44]There will be no restrictions on their age, sex, race, education, economic status, Kellgren-Lawrence score or Outbridge score.[45 46]

Types of Interventions

The eligible intervention is acupuncture including manual acupuncture and electroacupuncture. There will be no restriction on the sessions of acupuncture, needling techniques or stimulation methods.

Types of control groups

In this review, we plan to compare needle acupuncture with sham acupuncture, analgesic, usual care or waiting list control groups. Acupuncture plus one or more therapies with the same therapies also will be included.

Outcomes

Primary outcome

Pain intensity: The WOMAC Pain Subscale, Visual Analog Scale (VAS), Brief Pain Inventory (BPI), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) or other validated outcome measures.

Secondary outcomes

1. Function: The WOMAC Function Subscale, Lysholm Scale or other validated scales.

2. Quality of life: The 12-Item Short Form Health Survey (SF-12), 36-Item Short Form Health Survey (SF-36), Assessment of Quality of Life Instrument (AQoL II) or other validated scales.

3. Adverse events: Incidence and severity of adverse events

4. Drug use: Number of people using emergency analgesics, frequency or dosage of medication for KOA.

5. Cost: incremental cost-effectiveness ratio of acupuncture treatment

Criteria for excluding studies in this review

1. Participants with knee pain but no other criteria of KOA;

2. The intervention group received transcutaneous electrical nerve stimulation;

3. Studies reported only improvement rates;

4. Studies comparing one type of acupuncture with other type of acupuncture (except EA versus MA) and studies comparing acupuncture with complementary therapies or TCM.

Search methods for identification of studies

Electronic searches

We developed search strategies for four English databases (PubMed, Embase, Cochrane Library databases, and Web of Science) and four Chinese databases (China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP

Database for Chinese Technical Periodicals, and Wanfang) from database inception to September 1, 2021. Additional trials will be identified by searching previous systematic reviews. No language or publication status restrictions are applied. The search strategy components are clinical condition (osteoarthritis, chondromalacia patellae, knee, knee pain, and gonarthrosis), intervention (acupuncture, electroacupuncture, and acupuncture points) and study type (randomized controlled trial). We will adapt the search strategies to medical subject headings terms and keywords as necessary for each database (see appendix 2 for the search strategy used in the PubMed database). A pilot of the systematic search was conducted on 28 February 2021 (see appendix 3). We (F-TY and C-YL) will rerun the searches before submission of the manuscript to identify any eligible articles published since our first search.

Searching other sources

We will search the following websites as a supplement: the WHO International Clinical Trials Registry Platform and the National Institutes of Health clinical registry ClinicalTrials.gov and the Chinese Clinical Registry. The search will also include a manual search for gray literature (e.g., unpublished conference articles).

Data collection and analysis

Selection of studies

All search results will be exported to EndNote, where we will check for and exclude duplicates. Two of us will screen all titles and abstracts independently to identify potentially relevant studies. Full texts will be downloaded and printed for further

assessment. Two reviewers will screen the whole-length articles to confirm whether the studies meet the inclusion criteria. Any disagreement will be settled by discussion. If an agreement cannot be reached, a third reviewer will be consulted. The reasons for excluding studies will be recorded. The study selection process is shown in figure 1. Besides, we will add a table of exclude studies with reasons for exclusion to the appendix of our meta-analysis.

Data extraction and management

All data will be extracted independently and in duplicate by two reviewers with a predesigned data extraction template. Disagreements will be settled by discussion. A third reviewer will be consulted if discrepancies cannot be resolved. All data will be cross-checked by two reviewers and transferred into Microsoft Office Excel. If required, we will contact the corresponding authors for more information by email.

The predefined variables for extraction are the following:

1. Publication details (study year, first author, funding source);

2. Basic information (location, study type, number of centers, sample size, study duration, and length of follow-up);

3. Participants (type and/or stage of KOA, mean age, sex, and pain intensity before treatment);

4. Interventions (type of acupuncture, choice of acupuncture points, number of sessions, treatment frequency, duration of each session, and needling techniques)

5. Control (if there is any control, details of the treatment, including the name, dosage, frequency and course);

6. Outcomes (data and time points for each measurement, type and number of adverse events in each group).

Risk of bias assessment in included studies

Two reviewers will assess the risk of bias in the included studies by using the Cochrane Collaboration's tool for assessing risk of bias. We will assess each RCT a low, high, or unclear risk of bias for 6 domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of researchers and participants), attrition bias (incomplete outcome data), ascertainment bias (blinding of outcome assessment), reporting bias (selective outcome reporting) and other sources of potential bias. Disagreements will be resolved by discussion, according to the published articles and supplementary materials. We will consult the third reviewer and contact the study authors when needed.

Acupuncture adequacy assessment

We will use the adequacy assessment instrument to assess treatment adequacy in acupuncture RCTs from the following 4 aspects of acupuncture treatment: choice of acupuncture points, number of sessions, needling technique, and experience of the acupuncturists[47]. Two assessors who are experienced acupuncturists will assess adequacy independently and reach an agreement by discussion. They will be blinded to the results of the study and the publication and conduct the assessments only based on the description of the study population and the acupuncture procedure. To test the success of the blinding, we will ask the assessors to guess the identity of each study.

Heterogeneity assessment

If there are sufficient data, we will conduct a meta-analysis to determine the efficacy of acupuncture and the related factors. I^2 testing will be used to quantify heterogeneity among the included studies.[48] We will present summary estimates in forest plots. If the I^2 is more than 50%, we will explore the possible sources of heterogeneity via meta-regression and subgroup analyses. If a meta-analysis is not appropriate, we will conduct a descriptive synthesis using a best-evidence synthesis approach.

Reporting bias assessment

We will also consider assessing the reporting bias and small-study effects by using funnel plots when there are 10 or more trials. We will assess funnel plot asymmetry by using Begg's and Egger's tests and will define significant publication bias as a p value < 0.1. We will also use a trim-and-fill computation to estimate the effect of publication bias on the interpretation of the results.[49]

DATA SYNTHESIS

When the meta-analysis is performed, Stata 16.0 and RevMan 5.3 will be used for all statistical calculations. All the analyses will be based on the random-effects model because the RCTs included by us came from different populations. For dichotomous variables, Mantel-Haenszel method will be used for analyses and effect size will be reported as relative risk (RR) with 95% confidence intervals (CIs). For continuous variables, inverse variance method will be used for analyses and treatment effect will be reported as mean difference (MD) with 95% CIs. The standardized mean difference (SMD) with 95% CIs will be used if different scales are used to evaluate a predesigned outcome.

For pain variance, we plan to pool data from previous studies reporting VAS 100 mm, VAS 10 cm, and NRS by transforming it to a "0-100-pain measure" using an appropriate multiplier. We also intend to analyze pain intensity by independently reporting the aforementioned scales.

SUBGROUP ANALYSIS

Subgroup analyses will be performed to explain the heterogeneity. Predefined subgroups include the location of studies, the type of intervention, the dosage of acupuncture, the stage of knee osteoarthritis, and the TCM types of KOA.

SENSITIVITY ANALYSIS

We will conduct a sensitivity analysis to verify the robustness of the review conclusions. We will consider removing one study at a time to observe its effect on heterogeneity and effect size. In addition, the meta-analysis will be repeated after studies with lack of allocation concealment are excluded.

OTHER ANALYSIS

If manual acupuncture and eletroacupuncture are effective for KOA compared with sham acupuncture, we will conduct the exploratory research to compare the difference in the effectiveness between MA and EA by synthesizing the evidence from direct comparison and indirect comparison. For direct comparison results, we will use Revman to analyze. For the indirect comparison, we will choose sham acupuncture as a common comparator and use R software to analyze. Finally, we will conduct a mixed treatment comparison meta-analysis (MTC) to synthesize the evidence from direct comparison and indirect comparison.

Strength of recommendations and the quality of evidence

We will assess the strength of recommendations based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) working group methodology. The two categories of weak/conditional evidence and strong evidence will be used.

We will also assess the quality of evidence. The quality of evidence will be assessed according to the domains of risk of bias, consistency, directness, precision, and publication bias. The assessments will be adjudicated into four levels: high, moderate, low or very low.[50 51]

DISCUSSION

This systematic review will be performed based on previous studies of acupuncture for knee osteoarthritis. Conclusions drawn from this review may be beneficial to patients with KOA, clinicians and policy makers. We will summarize and explain the characteristics and findings of the included studies by conducting a systematic narrative synthesis.

Based on the above, we want to conduct some exploratory studies. (1) Is there a difference in the effectiveness between manual acupuncture and electroacupuncture? (2) Is the efficacy (if any) related to the stage of knee osteoarthritis according to the Kellgren-Lawrence score or Outbridge score, some characteristics of acupuncture (e.g., treatment frequency), type of control group, measurement time points of outcomes or other variables?

Manual acupuncture and electroacupuncture are the most commonly used

acupuncture therapies. Manual acupuncture maintains a moderate dose of stimulation by lifting, inserting and twisting needles to acupoints. However, it is laborious and difficult to reach an agreement on standards because of the different needle techniques. Electroacupuncture, which is widely used in clinical practice, refers to the pulse current input to acupoints on the basis of needle acupuncture. This approach can accurately control the dose of stimulation and save labor. In clinical trials for pain conditions, better analgesia appears to be obtained when electrical stimulation is added to manual stimulation than with manual acupuncture needle stimulation alone.[52] However, the findings may not be generalizable because of the different pain types.

There are many factors affecting the efficacy of acupuncture. One review presented "the challenge of adequacy of dose" recently.[33] Our group built a scoring instrument to calculate the dose of acupuncture from four parameters.[53] Based on the sum of the scores, we defined three doses of acupuncture treatment: high dosage, medium dosage and low dosage. And we designed three subgroups according the three kinds of dosage to explore the relationship between doses of acupuncture and efficacy. Deqi response is a comprehensive sensation of soreness, numbness, heaviness, aching at and around acupoints produced by manipulation of the needles. It plays a role in acupuncture dosage so it is only one dimension of our scoring instrument. On the one hand, not all types of acupuncture need a Deqi response during sessions. For example, manual acupuncture and electroacupuncture are required to cause a Deqi response while wrist-ankle acupuncture is not. Furthermore, electrical stimulation can enhance

Deqi response elicited by manipulation of needles. Based on the different duration of active stimulation, it is necessary to compare the effectiveness of manual acupuncture and electroacupuncture.[54] On the other hand, Deqi response is more emphasized in China than Western.[55]

Acupuncture has both specific effects caused by intervention itself and non-specific effects including patient-acupuncturist relationship, patient expectations, etc. Sham acupuncture group has usually been set in order to eliminate non-specific effects. The sham acupuncture can be divided into superficial insertion and non-penetrating insertion at traditional acupuncture points or not.[56] Superficial insertion is not a physiologically inert procedure and thus decreases the difference between groups.[57] Therefore, more and more trials choose non-penetrating sham acupuncture at non-acupoints as control to minimize the physiological effects of sham acupuncture.

The proposed review has several strengths. We plan to search multiple Chinese and English language databases to ensure a comprehensive search of the literature. Any meta-analyses will be performed according to the Cochrane Handbook for Systematic Reviews of Interventions. A further strength is that stringent eligibility criteria will be applied to ensure the quality of the included RCTs. In addition, pain intensity was selected as the targeted outcome because it plays an important role in the pain management of KOA. Transformation of pain scores measured by different pain scales to a 0-100 pain measure will result in loss of some accuracy; however, we believe that it is clinically irrelevant.

Ethics and dissemination

Ethics approval is not required because individual patient data are not included. This protocol was registered in the international Prospective Register of Systematic Reviews on 25 February 2021. The systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal. The findings will also be disseminated through conference presentations.

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Contributors C-YL is the guarantor and first author of the protocol. C-YL and L-QW designed the systematic review. C-YL and L-LL drafted the manuscript. J-WY, J-FT, L-QW and Myeong Soo Lee provided help to design and edited the manuscript. C-YL and F-TY will independently screen the eligible studies. C-YL and X-WH will extract data from included articles. J-LL and J-FT will assess the risk of bias. C-YL and X-TS will assess acupuncture adequacy, Strength of recommendations and the quality of evidence. C-YL, L-YQ and S-YY will finish data synthesis. L-QW will arbitrate any disagreements during the review. All authors have read the manuscript and approved the final publication of the protocol.

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Figure legends

Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

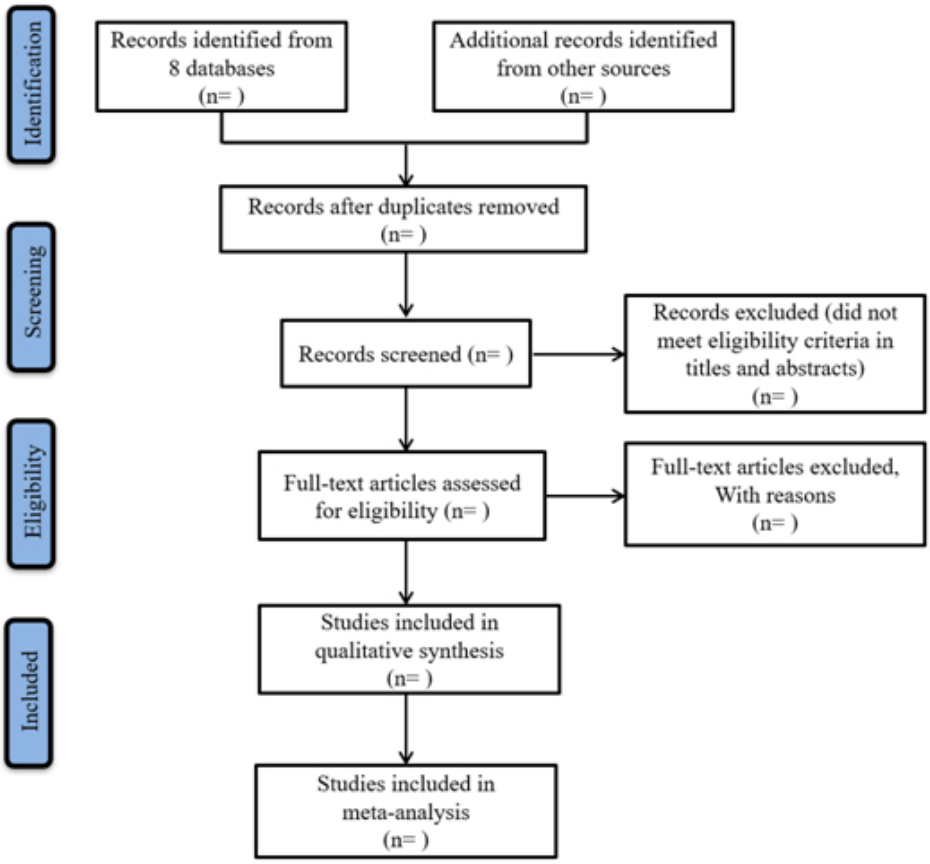

Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

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

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
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
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
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	10-11
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	10-11 Appendix2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12

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)	11-12
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	12
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	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
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 I^2, Kendall's τ)	14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

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

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

Table 1 Search strategy used in the PubMed database

#	Searches
1	Osteoarthritis, Knee[mesh]
2	Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract]
3	Patellofemoral Pain Syndrome[mesh]
4	Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract]
5	knee pain[Title/Abstract]
6	gonarthrosis[Title/Abstract]
7	OR/1-6
8	Acupuncture[mesh]
9	Pharmacopuncture[Title/Abstract]
10	Acupuncture Therapy[mesh]
11	Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract]
12	Electroacupuncture[mesh]
13	Acupuncture Points[mesh]
14	Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract]
15	OR/8-14
16	clinical[tiab]
17	trial[tiab]
18	16 AND 17
19	clinical trials as topic[mesh]
20	clinical trial[pt]
21	random*[tiab]
22	random allocation[mesh]
23	therapeutic use[sh]
24	OR/18-23
25	7 AND 15 AND 24

Result of presearch in the PubMed database

1. Osteoarthritis, Knee[mesh] Items found: 21,147
2. Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract] Items found: 40,291
3. Patellofemoral Pain Syndrome[mesh] Items found: 934
4. Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract] Items found: 3,799
5. knee pain[Title/Abstract] Items found: 8,083
6. gonarthrosis[Title/Abstract] Items found: 1,095
7. OR/1-6 Items found: 47,408
8. Acupuncture[mesh] Items found: 1735
9. Pharmacopuncture[Title/Abstract] Items found: 211
10. Acupuncture Therapy[mesh] Items found: 25,321
11. Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract] Items found: 2996
12. Electroacupuncture[mesh] Items found: 4128
13. Acupuncture Points[mesh] Items found: 6934
14. Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract] Items found: 6,284
15. OR/8-14 Items found: 27,954
16. clinical[tiab] Items found: 3,720,276
17. trial[tiab] Items found: 638,665
18. 16 AND 17 Items found: 294,477
19. clinical trials as topic[mesh] Items found: 353,132
20. clinical trial[pt] Items found: 884,322
21. random*[tiab] Items found: 1,202,203
22. random allocation[mesh] Items found: 104,737
23. therapeutic use[sh] Items found: 4,516,532
24. OR/18-23 Items found: 5,668,908
25. 7 AND 15 AND 24 Items found: 397

Final Result: 397 (By 28 February 2021)