

Effectiveness and safety of massage for chronic pain in patients with knee osteoarthritis

A protocol for systematic review and meta-analysis

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Abstract

Background: Chronic pain (CP) is a common and debilitating symptom in patients with knee osteoarthritis (KOA). Massage has been supported as a non-pharmacological intervention for the individual symptom relief of CP. However, relevant evidence of using massage for CP in patients with KOA has been lacking.

Methods: A systematic search will be performed in the following electronic databases for randomized controlled trials to evaluate the effectiveness and safety of massage for CP of KOA: China National Knowledge Infrastructure (CNKI), Wan Fang, PubMed, EMBASE, PsycINFO, and the Cochrane Library databases from their inception to December 2021. The entire process will include study selection, data extraction, risk of bias assessment and meta-analysis.

Results: This proposed study will evaluate the effectiveness and safety of massage for CP in patients with KOA. Changes in pain relief and adverse effect will be included in our outcomes.

Conclusions: This systematic review will provide evidence for assessing the credibility of massage for CP in patients with KOA.

Dissemination and ethics: The results of this review will be disseminated through peer-reviewed publication. This review does not require ethical approval because all of the data used in this systematic review and meta-analysis have already been published. Furthermore, all of these data will be analyzed anonymously during the review process.

Abbreviations: CI = confidence interval, CP = chronic pain, INPLASY = International Platform of Registered Systematic Review and Meta-analysis Protocols, KOA = knee osteoarthritis, RCTs = randomized controlled trials.

Keywords: chronic pain, knee osteoarthritis, massage, meta-analysis, protocol

JX and BW have made equal contributions.

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The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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1. Introduction

Knee osteoarthritis (KOA) is a common and disabling condition that typically manifests as attacks of pain around the joints, and it is a typical disease which can develop chronic pain (CP).^[1–3] The morbidity of KOA is quite high among the old. It is reported that 30% to 50% of people over the age of 60 suffer from KOA.^[4] Such a high incidence leads to a huge personal and socio-economic burden.^[5] The patient's ability to move is limited by CP,^[6] which further leads to the aggravation of pain symptoms.^[7] CP is one of the most common symptoms in patients with KOA.^[8] 25% of KOA patients suffer from severe joint pain.^[9] CP is defined as pain that lasts more than 3 to 6 months.^[10–12] Patients with CP are more likely to suffer from depression, anxiety, and insomnia.^[13–16]

Nondrug therapies is one of the treatments recommended by various guidelines for KOA.^[17,18] Current trials show that massage therapy is an effective nondrug intervention,^[19] which is possible to be more flexible in dealing with different clinical manifestations of CP in patient with KOA. There is evidence that massage has a positive effect on the treatment of KOA symptoms, such as pain without a specified course, stiffness and dysfunction.^[20] Massage does not have any major risks or side effects, and has the characteristics of high security, low cost, and convenient operation,^[21] and it has certain advantages for patients with drug allergy.^[22] This systematic review will attempt to provide a basis for evaluating the credibility of massage therapy in patients with CP caused by KOA.

Table 1**Search terms used in Pubmed database.****Search strategy**

#1 Intervention: (((((((((((((((((((((Massage[MeSH Major Topic]) OR (Zone Therapy)) OR (Therapies, Zone)) OR (Zone Therapies)) OR (Therapy, Zone)) OR (Massage Therapy)) OR (Massage Therapies)) OR (Therapies, Massage)) OR (Therapy, Massage)) OR (Manipulations, Musculoskeletal)) OR (Manipulation Therapy)) OR (Manipulative Therapies)) OR (Manipulative Therapy)) OR (Therapies, Manipulative)) OR (Therapy, Manipulative)) OR (Therapy, Manipulation)) OR (Manipulation Therapies)) OR (Therapies, Manipulation)) OR (Reflexology)) OR (Bodywork)) OR (Bodyworks)) OR (Rolfing)) OR (Craniosacral Massage)) OR (Massage, Craniosacral)) OR (Manual Therapies)) OR (Manual Therapy)) OR (Therapies, Manual)) OR (Therapy, Manual)

#2 Participant: (((((((((((((((((((((Chronic Pain[MeSH Major Topic]) OR (Chronic Pains)) OR (Pains, Chronic)) OR (Pain, Chronic)) OR (Widespread Chronic Pain)) OR (Chronic Pain, Widespread)) OR (Chronic Pains, Widespread)) OR (Pain, Widespread Chronic)) OR (Pains, Widespread Chronic)) OR (Widespread Chronic Pains)) AND (((Osteoarthritis, Knee [MeSH Major Topic]) OR (Knee Osteoarthritis)) OR (Knee Osteoarthritis)) OR (Osteoarthritis of Knee)) OR (Osteoarthritis of the Knee))

#3 Study design: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [tiab]) NOT (animals [mh] NOT humans [mh])

#4 #1 AND #2 AND #3

Meta-analysis is a powerful statistical technique and is widely accepted as an important tool of evidence-based medicine. So far, there is no evidence for massage to be used for CP in patients with KOA for more than 6 months. Therefore, we perform this protocol to comprehensively assess the effect of massage for CP in patients with KOA, which will attempt to provide a basis for evaluating the credibility.

2. Methods

2.1. Study registration

This protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) on December 19, 2021 (registration number: INPLASY2021120087). We will strictly perform this protocol by following the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol statement guideline.

2.2. Criteria for included studies

We will conduct a comprehensive search of China National Knowledge Infrastructure (CNKI), WanFang, PubMed, EMBASE, PsycINFO, and the Cochrane Library databases from their inception to December 2021.

The inclusion criteria are as follows:

- Only randomized controlled trials (RCTs) about massage for CP by KOA will be included, with language restrictions in English or Chinese. Case report, experience report, and laboratory studies will not be included.
- All patients with CP over 6 months will be included without limitation of age, race, gender, economic level, and severity.
- The interventions of experimental group will only consist of massage therapies, mainly including general massage, acupressure, Chinese massage, relaxation, manual lymphatic drainage and so on. There will be no limitation on the methods, duration, and frequency of massage.
- The interventions of control group will involve any therapy other than massage (e.g., medication, placebo, routine care, etc).

2.3. Outcome

Primary outcomes: Western Ontario McMaster Osteoarthritis Index pain subscore.

Additional outcomes:

- WOMAC Stiffness subscore, Physical Function subscore and global score.
- Visual analogue scale.
- A 12-item Short-Form Health Survey (SF-12).
- Pressure pain threshold.
- Numerical rating scale of soreness intensity.
- Adverse events.
- Frequency of delayed onset of muscle soreness.

2.4. Search strategy

We will perform a comprehensive search in PubMed, the Cochrane Library, EMBASE and 4 Chinese databases (CNKI, Wan Fang, CBMdisc, and VIP) for articles published before December, 2021. Only RCTs that used massage as the main treatment for adults with athletic injuries will be included. The Chinese and English search strategies in PubMed database are shown in Table 1. The search terms in the Chinese databases have the same meaning as those used in the English databases. There will be no language restrictions in this review.

2.5. Identification of studies

All the search results will be imported into NoteExpress v3.5.0.9054 for management. Two reviewers (JX and YF) will independently screen all potentially eligible studies. Titles and abstracts will be screened first to exclude irrelevant citations. Full text of all the articles with potentially relevant abstracts will be retrieved and screened according to the study eligibility criteria. Disagreements will be resolved by consensus or discussion with a third reviewer (GG). The research flow chart is shown in Figure 1.

2.6. Data collection

Two reviewers will extract data from the included literature through Microsoft Excel 2010 (Microsoft company, Seattle, WA), mainly including the following information (Table 2):

- General information about the study, such as authors, year of publication, country, groups, sample size, age, and gender.
- Detailed treatment information, such as diagnostic criteria and parameters of intervention.
- Pain scores. Other outcome measurements, such as SF-12 or Frequency of delayed onset of muscle soreness, will be extracted if they are mentioned in the study.

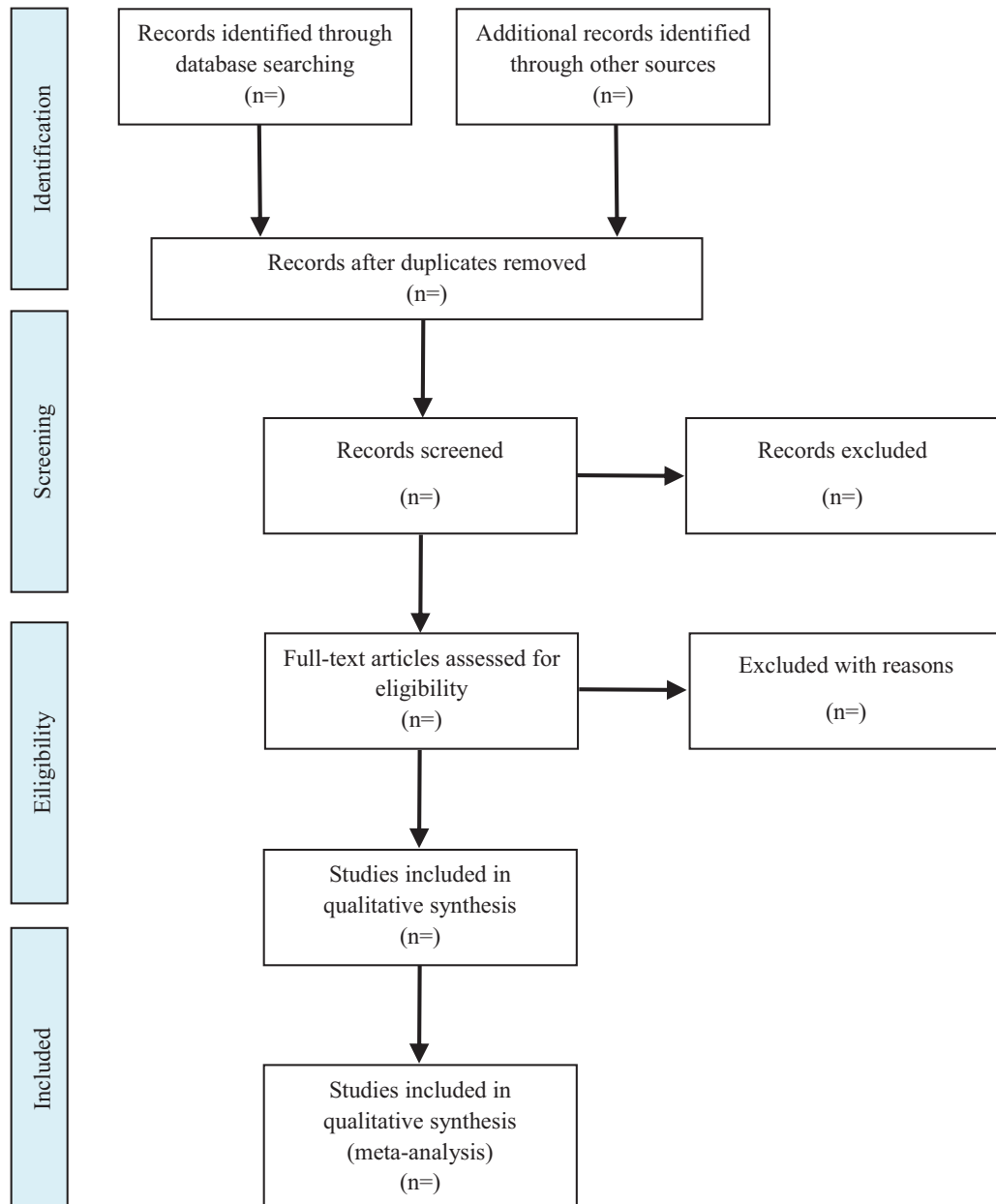


Figure 1. This figure is a flow diagram of study selection. A. Searching the literature in databases. B. Screening of the title and abstract of the articles. C. Choosing the eligible studies. D. Including the studies which is in qualitative synthesis.

- Duration of the pain.

quality.^[23] In addition, we will use the online guideline development tool to conduct this process.

2.7. Quality of evidence assessment

Based on Grading of Recommendations Assessment Development and Evaluation, we will assess the quality of evidence as 4 grades: high quality, moderate quality, low quality, and very low

2.8. Risk of bias assessment

Study quality will be assessed in RevMan V5.4.1 (the Nordic Cochrane Centre, Cochrane Collaboration) using the Cochrane

Table 2
Data extraction form.

First authors	Year	Country	Sample size	Mean age
Gender	Pain location	Duration	Follow-up	Diagnostic criteria
Experimental group intervention	Control group intervention	Main outcome assessments		

risk of bias tool.^[24] The risk of bias for each of the following domains will be assessed for each study: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other bias. Each study included will be rated as having a high, low, or unclear risk of bias. Two reviewers (JX and BW) will evaluate the consistency of all the extracted data and quality ratings. Disagreements will be resolved by discussion with a third reviewer (GG).

2.9. Statistical analysis

Revman 5.4 software will be used to perform statistical analysis. For discontinuous variables, the risk ratio with 95% confidence interval (CI) will be selected. For continuous variables, the weighted mean difference with 95% CI will be selected when the measuring instruments are the same, and the standardized mean difference with 95% CI will be selected when the measuring instruments are different. We will use the fixed-effect model if there is no significant heterogeneity ($P > .1$ or $I^2 < 50\%$). If there is a significant heterogeneity ($P > .1$ or $I^2 < 50\%$), we will conduct subgroup analysis or sensitivity analysis to identify possible causes of heterogeneity among populations.

2.10. Subgroup analysis

If the necessary data are available, subgroup analysis will be conducted according to the following criteria^[25]:

- The treatment period.
- Different acupuncture points with massage.
- Different types of manipulation (e.g., kneading, rolling, pressing).

2.11. Subgroup analysis

To identify the robustness of the meta-analysis, low-quality trials, with high risks of bias or outcomes that are seriously distant from the rest of the data, will be excluded.

2.12. Ethics and dissemination

Ethical approval will not be in need because the data used in this systematic review will not be individual patient data, and there will be no concerns regarding privacy.

3. Discussion

Quality of life of a large number of patients with KOA is reduced by CP.^[5] The mechanism of CP in KOA is complex and the degree of pain may be inconsistent with the local abnormal pathological manifestations of the knee.^[26] At molecular level, an animal model study shows that inflammation contributes to the evolution of joint tissue degradation and remodeling as well as joint pain.^[27,28] On the structural image, CP can cause more bad experiences and induce changes in brain structure and brain function related to emotion. The reorganization of functional brain network structures such as thalamus, periaqueductal gray (PAG), anterior cingulate cortex (ACC) and prefrontal cortex (PFC) is closely related to KOA-related CP.^[29–34] Emotion can in turn aggravate the pain experience.^[35] At biomechanical aspect, a study compared the walking gait biomechanics of patients with

KOA after intensive intervention of lower extremities. Fifty-three patients with KOA had slight changes in their knee flexion angle (KFA) due to the enhancement of lower limb muscle strength 10 times in 28 days.^[36]

Massage in the treatment of KOA has a history of thousands of years in China.^[37] The efficacy of massage in the treatment of KOA has been confirmed by some RCT.^[20,38] A study found that massage can change the expression of RANTES and MCP-1 and improve the symptoms of KOA.^[27] The latest research also points out that massage can not only remove neutrophils from seriously injured muscle tissue, but also eliminate inflammatory factors released during the process, thus promoting the regeneration of muscle fibers.^[39] It can also adjust the changes of pain-related brain function network.^[30,34,40] A study of 72 KOA patients shows that 36 times massage in 12 weeks can improve the soft tissue tension, adjust the structural relationship of the knee joint, make the tibial angle tend to normal range to balance local mechanics, reduce the degree of varus deformity and reduce the pain of patients.^[41] A study of 18 female patients with KOA shows that 6 weeks of massage plus exercise is more beneficial to blood circulation, muscle tension, and flexibility than only exercise,^[28] thus improving patients' mood and quality of life. An increasing number of studies have demonstrated that massage has beneficial effects on symptom management in patients with KOA^[28,42]; however, almost all the studies focused on pain without time limit. And there is a widespread lack of identification of the most effective massage treatment for CP.

Therefore, this online meta-analysis will provide a detailed summary and analysis of the latest evidence, with a focus on the available massage methods. We hope that our findings will help patients, clinicians and health care policy makers make better treatment choices for CP.

Author contributions

JX, YF, and BW conceived the study. SX, HZ, GW, and GG provided general guidance to the drafting of the protocol. JX and BW drafted the protocol. GW and SX designed the search strategy. GG, BW, and JX drafted the manuscript. SX, HZ, BW, GW, YF, JX, and GG reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

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