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A comparison of the effects of Chinese non-pharmaceutical therapies for pain control in knee osteoarthritis
A protocol for a systematic review and network meta-analysis

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Abstract

Background: Knee osteoarthritis (KOA) is a chronic degenerative joint disease, leading to pain and functional limitation in the elderly. The non-pharmaceutical therapy is recommended firstly by different guidelines for KOA management strategies. In China, there are various forms of non-pharmaceutical treatments for KOA, which are considered beneficial in relieving KOA pain. However, there is no consensus on which is the optimal non-pharmaceutical regimens. Thus, present network meta-analysis aims to assess the comparative efficacy of available Chinese non-pharmaceutical therapies, especially in pain management.

Methods: PubMed, EMBASE, Cochrane library, Web of Science, China national knowledge infrastructure, VIP, Wan Fang will be systematically searched their inception to April 2020. Randomized controlled trials that compared the effect of non-pharmaceutical therapies on pain control in KOA will be included, including traditional acupuncture, electroacupuncture, warming needle, fired needle, acupuncture followed by moxibustion, moxibustion and massage. The primary outcome was the knee pain levels, and secondary outcome was the comprehensive indicators. Risk of bias assessment of the included studies will be performed according to the Cochrane risk of bias tool. The pairwise and network meta-analysis will be performed by STATA 14.0 and GeMTC softwares.

Results: This study is ongoing and will be submitted to a peer-reviewed journal for publication.

Conclusion: This study will provide a comprehensive evidence on the effects of Chinese non-pharmaceutical therapies for pain control in KOA.

PROSPERO registration number: CRD42018106575

Abbreviations: AM = acupuncture followed by moxibustion, EA = electroacupuncture, FN = fired needle, KOA = knee osteoarthritis, Mas = massage, Mox = moxibustion, RCT = randomized controlled trial, TA = traditional acupuncture, WN = warming needle, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Keywords: acupuncture, knee osteoarthritis, massage, moxibustion, network meta-analysis, non-pharmaceutical therapy

1. Introduction

Knee osteoarthritis (KOA) is a chronic degenerative joint disorder among older adults, leading to pain, stiffness, and functional limitation.[1] Cross[2] reported the global prevalence of symptomatic KOA in 2010 was 3.8%. However, the incidence of KOA may be higher in developing countries such as China (8.1%)[3] and India (28.7%).[4] Such high incidence leads to a tremendous individual and socioeconomic burden for all

countries,[5] especially in the economically less-developed regions.

Pain caused by KOA can have a significant impact on the progression of the disease, because it can limit the mobility of patients,[6] and cause psychosocial problems such as low self-efficacy and depression.[7] These challenges can lead to a considerable decline in the quality of life. Thus, the current therapeutic approaches for KOA recommended by various guidelines are often divided into 3 main categories: non-pharmacological, pharmacological, and surgical,[8–11] which are primarily aimed at minimizing joint pain and optimizing function.[12]

Non-pharmacological approaches were first recommended and considered to be crucial in managing chronic knee pain.[9] With the exception of patient education, exercise and other non-pharmacological therapies in China are similar to those recommended in European and American guidelines. These non-pharmacological strategies include Traditional Chinese Medicine acupuncture, moxibustion, (Mox) and tuina or massage (Mas), which are recommended by the Rheumatology Society[13] and Orthopaedic Society[14] of the Chinese Medical Association.

Acupuncture is probably the most widely recognized complementary and alternative medicine worldwide, with origins in ancient China.[15] The effectiveness of acupuncture in the treatment of pain has been confirmed in cases of musculoskeletal disorders, headaches, and osteoarthritis.[16] However it remains controversial, largely due to a lack of evidence for the underlying mechanism.[17]

Mox is an ancient form of thermotherapy widely used in East Asia. It entails the use of direct or indirect burning of dried mugwort on special acupoints. Existing evidence supports the effectiveness of Mox in the treatment of OA pain, and although results have been , they are far from conclusive.[18,19] Since ancient times, Chinese acupuncture methods have led to other combined treatment derivatives, which relieve KOA pain. These derived methods are based on traditional acupuncture (TA) and include electroacupuncture (EA), which combines TA with electrical stimulation, and the warming needle (WN), which combines TA with Mox.

Another non-pharmacological intervention, Mas, is also widely used. In 2012, 15.4 million Americans reportedly used Mas to treat OA.[20] Some randomized controlled trials (RCT) have further verified the efficacy of Mas in KOA.[21,22] Although the effectiveness of these complementary interventions has been reported in many studies, determination of the most effective therapies among non-pharmacological treatments are generally lacking in the field of CAM.

Meta-analysis is a powerful statistical technique, widely accepted as an important tool in evidence-based medicine.[23] Although several direct meta-analyses have been conducted to validate the effectiveness of acupuncture,[24] EA,[25] and Mox[26] in KOA, no relevant review or meta-analysis currently exists among all Chinese non-pharmaceutical therapies. Bayesian network meta-analysis could combine all direct or indirect evidence from different treatment comparisons to facilitate the compilation of a unified, coherent analysis of all trials.[27,28] Therefore, the aim of this network meta-analysis was to assess the comparative efficacy of available Chinese non-pharmaceutical therapies in pain management, with the purpose of providing comprehensive and reliable evidence-based medical evidence in clinical practice.

2. Methods

2.1. Study registration

The proposed systematic review will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement guidelines.[29]

This systematic review and network meta-analysis protocol has been registered on the PROSPERO 2018 (ID: CRD42018106575).

2.2. Study eligibility criteria
2.2.1. Type of studies.
Only RCTs containing TA, EA, WN, fired needle (FN), acupuncture followed by moxibustion (AM), Mox or Mas against another or against placebo/sham in patients with KOA will be included in this review. Non-randomized studies or patients after knee replacement will be excluded.

2.2.2. Type of participants.
Studies that enrolled patients of any age, gender with a clinical diagnosis of KOA will be included.

2.2.3. Type of interventions.
We will consider studies evaluating the following treatments: any type of TA, EA, WN, FN, AM, Mox, or Mas used as the sole treatment for KOA, and compared control comparators such as pharmacological treatment or no treatment/placebo, which act as vital arms for the incorporation of indirect evidence in the networks.

2.2.4. Types of outcome measures
2.2.4.1. Primary outcomes.
Knee pain levels will be assessed by the visual analogue scale [30] the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score pain sub-scale[31] or the 11-point numeric rating scale.[32]

2.2.4.2. Secondary outcomes.
Comprehensive indicators will be assessed by the WOMAC total scores or the 36-item Short-Form Health Survey for quality of life. In addition, relevant adverse events will be recorded. In addition, relevant adverse events will be recorded.

2.3. Search strategy

We will electronically search the following databases from their inception through April 2020: Pubmed, Embase, Cochrane library, Web of science, the China National Knowledge Infrastructure, VIP Information and Wanfang Data. The search approach will use a combination of subject word (keyword) and random words related to KOA, interventions of interest (TA, EA, WN, FN, Mox, AM, Mas, sham/placebo), and RCTs. The search words in the Chinese databases have the same meaning as those used in the English databases. To ensure that the most recent trials will be included, we will also retrieve unpublished protocols and summary results through a search of the clinical trial registry at https://clinicaltrials.gov/. In addition, we will search the previously published reviews and meta-analysis related to KOA using TA, EA, WN, FN, Mox, AM or Mas. There will be no language restrictions in this review.

2.4. Identification of studies

The search results from above 7 databases will be imported to ENDNOTE X7 software to data management. After being trained specifically for this study, 2 reviewers (XW Shi and WJ

Yu) will screen the articles independently for possible candidates based on the inclusion and exclusion criteria. Any duplicate studies will be removed. After passing the title and abstract screening, the full-text copies of all eligible studies will be downloaded for re-evaluation. A third reviewer (DF Wang or Y Zhao) will consult in cases of disagreement between the first 2 reviewers and rechecked the included studies. Excluded studies and the reasons of exclusion will be recorded.

2.5. Data collection

After identification of the target RCTs, 2 independent reviewers (WJ Yu and C Chen) will extract the necessary data using a customised form created by Microsoft Excel 2010 (Microsoft Company, USA, Seattle). One reviewer (XW Shi) will check the accuracy and consistency of all extracted data. The following data will be extracted:

(1) the general information of study such as the authors, year of publication, country, groups, sample size, age, sex;
(2) the detailed treatment information such as diagnostic criteria, parameters of intervention;
(3) pain scores. Other outcome measurements such as WOMAC total scores or 36-item short-form health survey score will be extracted if the study is involved.

2.6. Quality of evidence assessment

According to Grading of Recommendations Assessment Development and Evaluation, we will assess the quality of evidence as 4 levels: high quality, moderate quality, low quality and very low quality.[33] In addition, we will use the online guideline development tool to conduct this process.

2.7. Risk of bias assessment

The Cochrane Risk of Bias tool,[34] which contains 7 specific domains: sequence generation, allocation concealment, blinding of participants and personnel and other aspects of bias, and the risk of bias of all included RCTs will be assessed with methodological quality as low risk, high risk, or unclear risk of bias. If any domain is scored high/low risk of bias, the study will be considered high/low risk of bias. Two reviewers (Y Zhao and XF Deng) will conduct the quality assessments separately, and a third reviewer (C Chen) will recheck the analyzed data.

2.8. Statistical analyses

Firstly, classic pairwise meta-analyses will be synthesized, using the Review Manager Software (version 5.0; the Cochrane Collaboration, Oxford, UK). The results will be reported as the mean difference with corresponding 95% confidence intervals. The Chi-squared test and I^2 test will be used to assess the heterogeneity across studies.

Secondly, a random-effects Bayesian network meta-analysis will be performed, using the GeMTC software (University Medical Center Groningen, The Netherlands) and the STATA software (version 14.0, StataCorp) for network meta-analysis. Network meta-analysis is a statistical technique used to integrate both direct and indirect evidence for comparisons of interest, which is commonly regarded as its main advantage.[35] Using a full Bayesian evidence network, all indirect comparisons were considered to arrive at a single, integrated, estimate of the effects of all included treatments based on all eligible studies. The Markov chain Monte Carlo method will be applied to calculate the pooled effect sizes. Significant differences were assessed using the upper and lower limits of 95% CIs, without consideration of the value 0. The inconsistency test will be verified using the node-splitting method. According to the quantitative estimation, we will adjust the inclusion of studies and ultimately obtain an ideal network with consistency.

Lastly, network meta-analysis was also able to generate rank probabilities (first, second, and third most effective, etc) for all treatments under evaluation. Probability values will be summarized and reported as the surface under the cumulative ranking (SUCRA).[36] The most effective treatment would have had a SUCRA equal to 100%, while the worst treatment, a SUCRA equal to 0%.[36,37]

3. Discussion

Typical manifestations of KOA, the most prevalent form of osteoarthritis in the lower limbs, include pain, and limited function.[38] Non-pharmaceutical therapy was first recommended the treatment of KOA by various current guidelines. In China, various forms of non-pharmaceutical therapies can treat KOA pain, including acupuncture (manual acupuncture, WN, and EA), Mox and Mas. Different forms of acupuncture are widely used to pain management of KOA in China, although the recommendations of acupuncture among different guidelines are controversial. Mox, entails the use of dried mugwort (mox) materials, and produces heat to stimulate specific acupoints, with the purpose of treating diseases.[39] It is frequently used in conjunction with acupuncture. It has been well documented that local heat application could reduce pain.[40,41] A recent meta-analysis reported that Mox for KOA was more effective than medication or sham treatments.[26] Mas therapy involves the application of pressure on the joints and muscles to maintain good health or relieve pain. It may be the oldest CAM with evidence of extensive use across most regions worldwide.[42] Although the effectiveness of these complementary interventions has been reported in many studies, determination of the most effective therapies among non-pharmacological treatments are generally lacking in the field of CAM. Thus, this network meta-analysis will provide a detailed summary and analysis of the latest evidence focusing on available Chinese non-pharmaceutical therapies (TA, EA, WN, FN, AM, Mox, or Mas) as well as relevant other treatments for pain management in KOA. Nonetheless, we hope that our findings will assist patients, clinicians and healthcare policy-makers to make a better choice of treatments in KOA, especially the application of non-pharmaceutical therapies in the complementary and alternative medicine.

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References

[1] Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. Arthritis Care Res (Hoboken) 2016;68:1743–50.

[2] Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323–30.

[3] Tang X, Wang S, Zhan S, et al. The prevalence of symptomatic knee osteoarthritis in China: results from the China Health and Retirement Longitudinal study. Arthritis Rheumatol 2016;68:648–53.

[4] Pal CP, Singh P, Chaturvedi S, et al. Epidemiology of knee osteoarthritis in India and related factors. Indian J Orthop 2016;50:518–22.

[5] Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol 2014;10:437–41.

[6] Van Tunen JAC, Dell'isola A, Juhl C, et al. Association of malalignment, muscular dysfunction, proprioception, laxity and abnormal joint loading with tibiofemoral knee osteoarthritis - a systematic review and meta-analysis. BMC Musculoskelet Disord 2018;19:273.

[7] Riddle DL, Kong X, Fitzgerald GK. Psychological health impact on 2-year changes in pain and function in persons with knee pain: data from the osteoarthritis initiative. Osteoarthritis Cartilage 2011;19:1095–101.

[8] Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of non-pharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64:465–74.

[9] Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72:1125–35.

[10] National Institute for Health and Care Excellence. Osteoarthritis: care and management. NICE guidelines [CG177] 2014;1–37.

[11] Mcalindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363–88.

[12] Dadabo J, Fram J, Jayabalan P. Noninterventional therapies for the management of knee osteoarthritis. J Knee Surg 2019;32:46–54.

[13] Association RSOCMGuidelines for diagnosis and treatment of osteoarthritis. Chin J Rheumatol 2010;14:416–9.

[14] Association OSOCMGuidelines for the diagnosis and treatment of osteoarthritis (2018 edition). Chin J Orthop 2018;38:705–15.

[15] De Luigi AJ. Complementary and alternative medicine in osteoarthritis. PM R 2012;4:S122–33.

[16] Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for chronic pain: update of an individual patient data meta-analysis. J Pain 2018;19:455–74.

[17] Vickers AJ, Linde K. Acupuncture for chronic pain. JAMA 2014;311:955–6.

[18] Choi TY, Choi J, Kim KH, et al. Moxibustion for the treatment of osteoarthritis: a systematic review and meta-analysis. Rheumatol Int 2012;32:2969–78.

[19] Choi TY, Lee MS, Kim JI, et al. Moxibustion for the treatment of osteoarthritis: an updated systematic review and meta-analysis. Maturitas 2017;100:33–48.

[20] Ernst E. Complementary and alternative medicine for pain management in rheumatic disease. Curr Opin Rheumatol 2002;14:58–62.

[21] Pehlivan S, Karadakovan A. Effects of aromatherapy massage on pain, functional state, and quality of life in an elderly individual with knee osteoarthritis. Jpn J Nurs Sci 2019;16:450–8.

[22] Perlman A, Fogerite SG, Glass O, et al. Efficacy and safety of massage for osteoarthritis of the knee: a randomized clinical trial. J Gen Intern Med 2019;34:379–86.

[23] Walker E, Hernandez AV, Kattan MW. Meta-analysis: its strengths and limitations. Cleve Clin J Med 2008;75:431–9.

[24] Lin X, Huang K, Zhu G, et al. The effects of acupuncture on chronic knee pain due to osteoarthritis: a meta-analysis. J Bone Joint Surg Am 2016;98:1578–85.

[25] Chen N, Wang J, Mucelli A, et al. Electro-acupuncture is beneficial for knee osteoarthritis: the evidence from meta-analysis of randomized controlled trials. Am J Chin Med 2017;45:965–85.

[26] Yuan T, Xiong J, Wang X, et al. The effectiveness and safety of moxibustion for treating knee osteoarthritis: a PRISMA compliant systematic review and meta-analysis of randomized controlled trials. Pain Res Manag 2019;2019:2653792.

[27] Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331:897–900.

[28] Mills EJ, Ioannidis JP, Thorlund K, et al. How to use an article reporting a multiple treatment comparison meta-analysis. JAMA 2012;308:1246–53.

[29] Shamseer L, Moher D, Clarke M, et al. Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.

[30] Crichton N. Information point: visual analogue scale (VAS). J Clin Nurs 2001;10:697–706.

[31] Theiler R, Spielberger J, Bischoff HA, et al. Clinical evaluation of the WOMAC 3.0 OA index in numeric rating scale format using a computerized touch screen version. Osteoarthritis Cartilage 2002;10:479–81.

[32] Farrar JT, Young JP, JR Lamoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–58.

[33] Puhan MA, Schunemann HJ, Murad MH, et al. A GRADE working group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2014;349:g5630.

[34] Higgins JP, altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[35] Cipriani A, Higgins JP, Geddes JR, et al. Conceptual and technical challenges in network meta-analysis. Ann Intern Med 2013;159:130–7.

[36] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.

[37] Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8:e76654.

[38] Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease study. Lancet 2016;388:1545–602.

[39] Choi SH, Chang IM. A milestone in codifying the wisdom of traditional oriental medicine: TCM, Kampo, TKM, TVM-WHO international standard terminologies on traditional medicine in the Western Pacific region. Evid Based Complement Alternat Med 2010;7:303–5.

[40] Yildirim N, Filiz Ulusoy M, Bodur H. The effect of heat application on pain, stiffness, physical function and quality of life in patients with knee osteoarthritis. J Clin Nurs 2010;19:1113–20.

[41] Karadag S, Tasci S, Dogan N, et al. Application of heat and a home exercise program for pain and function levels in patients with knee osteoarthritis: a randomized controlled trial. Int J Nurs Pract 2019;25:e12772.

[42] Stein DJ. Massage acupuncture, moxibustion, and other forms of complementary and alternative medicine in inflammatory bowel disease. Gastroenterol Clin North Am 2017;46:875–80.