INPLASY PROTOCOL

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Corresponding author:
Boyu Wu

dctgyt2008@163.com

Author Affiliation:
The First Affiliated Hospital of Hunan University of Chinese Medicine.

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Conflicts of interest:
None declared.

Traditional Chinese medicine therapies for patients with knee osteoarthritis: A protocol for systematic review and network meta-analysis

Wu, B[1]; Yang, L[2]; Fu, C[3]; Guo, Y[4].

Review question / Objective: **In this study, we will conduct an NMA to evaluate the efficacy and safety of various TCM therapies adopted in KOA treatment.**
Condition being studied: **KOA is a common degenerative joint disease that not only causes pain and physical disability but also poses a substantial economic burden on society. TCM has been recognized as one of the typical representatives of CAM, which are attracting increasing international attention. Meanwhile, there is increasing evidence that multiple TCM therapies can be safe and effective in patients with KOA. Meanwhile, an increasing number of clinical and experimental studies have confirmed that TCM can effectively relieve the pain of KOA and enhancing patients' quality of life. Currently, several conventional pairwise meta-analyses have investigated the comparative efficacy and safety of single TCM therapies for KOA. However, no NMA has been performed to evaluate the comparative efficacy and safety of all the available TCM therapies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 March 2022 and was last updated on 02 March 2022 (registration number INPLASY202230008).

INTRODUCTION

Review question / Objective: **Knee osteoarthritis (KOA) is a common chronic degenerative disease characterized by progressive damage of articular cartilage, subchondral bone re modeling, and secondary synovial inflammation. It is one of the leading causes of disability, seriously affecting patients' quality of life. KOA affects more than 250 million people worldwide , and will increase substantially with aging of the global population and the obesity epidemic. Therefore, KOA has emerged as a main global health problem and resulted in a substantial economic burden on the health care**

systems. According to international guidelines , the therapeutic drugs for KOA mainly include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, opioids, and steroid injections, which only alleviate symptoms but fail to block disease progression. Moreover, these drugs may lead to a series of side effects, including gastrointestinal bleeding, hepatic and renal toxicity, and cardiovascul ar complications, and hence long-term clinical use has been limited . Due to t he limitations and adverse effects associated with the existing pharmacological treatments, research into therapies for KOA in Complementary and alternative medicine (CAM) is receiving greater attention. Traditional Chinese medicine (TCM) is one of the most commonly used CAM modalities, including Chinese herbal medicine, acupuncture, moxibustion, tuina (Chinese massage), cupping and other forms, which may be administered alone or in combination. Its efficacy and safety have been confirmed through long-term clinical practice. Presently, accumulating evidence indicates that TCM can effectively improve the clinical symptoms in KOA patients with a high degree of safety and few side effects. However, due to a relatively small amount of direct head-to-head comparison studies between different types of TCM therapies, the comparative outcomes between TCM therapies are still inconclusive. Network meta-analysis (NMA) has been widely used in medical research, as it allows multiple interventions to be compared and ranked, overcoming the limitations of conventional pairwise meta-analyses. In this study, we will conduct an NMA to evaluate the efficacy and safety of various TCM therapies adopted in KOA treatment.

Condition being studied: KOA is a common degenerative joint disease that not only causes pain and physical disability but also poses a substantial economic burden on society. TCM has been recognized as one of the typical representatives of CAM, which are attracting increasing international attention. Meanwhile, there is increasing evidence that multiple TCM therapies can be safe and effective in patients with KOA. Meanwhile, an increasing number of clinical and experimental studies have confirmed that TCM can effectively relieve the pain of KOA and enhancing patients' quality of life. Currently, several conventional pairwise meta-analyses have investigated the comparative efficacy and safety of single TCM therapies for KOA. However, no NMA has been performed to evaluate the comparative efficacy and safety of all the available TCM therapies.

METHODS

Participant or population: Patients with knee osteoarthritis.

Intervention: Traditional Chinese medicine therapies.

Comparator: Western medicine or placebo.

Study designs to be included: Randomized control trials (RCTs).

Eligibility criteria: ① Types of studies. All randomized controlled trials (RCTs) on TCM therapies for KOA will be included. The languages of publication will be restricted to Chinese and English. We will exclude the following types of publications: case reports, case series, letters, comments, conference abstracts, reviews, animal studies and studies with incomplete data. ② Types of participants. We will include adult participants (≥ 18 years) diagnosed (based on radiographic evidence and clinical criteria) with KOA, irrespective of country, race, and gender. ③ Type of interventions and comparisons. In the experimental group, any form of TCM therapies will be included, such as Chinese herbal medicine, acupuncture, moxibustion, tuina (Chinese massage), cupping therapy, etc. In routine clinical practice, clinicians usually use a combined therapy to treat KOA, so the combination of different TCM therapies will also be included. Patients in the control group were treated with western m

edicine or placebo. Additionally, therapies combining western medicine with TCM will be excluded. ④ Types of Outcome Measures. The primary outcome measures were: Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, and Lequesne index. The secondary outcome measures were: total clinical effective rate and adverse events. Other outcomes will also be assessed if necessary.

Information sources: Five English databases (PubMed, Web of Science, EMbase, EBSCO, and Cochrane Library) and 4 Chinese databases (China National Knowledge Infrastructure, Wanfang, Chinese Biomedical Literature Database, and the VIP Database) will be searched.

Main outcome(s): Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, and Lequesne index.

Additional outcome(s): Total clinical effective rates and adverse events.

Quality assessment / Risk of bias analysis: The Cochrane risk of bias tool (RoB 2.0) will be used to assess the quality of studies.

Strategy of data synthesis: ① Pairwise meta-analysis. We will perform the pairwise meta-analysis on direct comparisons with STATA 15.0. Odds ratio (OR) with 95% confidence intervals (CI) will be applied for dichotomous outcomes, while mean difference (MD) or standard mean difference (SMD) with 95% CI will be calculated for continuous variables. Heterogeneity among studies will be assessed using the I-squarestatistic. A random effect model will be used if I2 > 50%, otherwise a fixed effect model will be applied. ② Network meta-analysis. We will conduct the NMA on indirect comparisons with WinBUGS 1.4.3 and STATA 15.0.
A random effects model will be employed to perform the NMA, considering the anticipated clinical heterogeneity among studies. The Brooks-Gelman-Rubin method will be used to examine the model convergence. Node-splitting method will be used to estimate the inconsistency by comparing the direct evidence with the indirect evidence. To obtain the ranking probability of the different treatments, the surface under the cumulative ranking curve (SUCRA) will be calculated.

Subgroup analysis: If heterogeneity or inconsistency among the studies is detected, subgroup analysis will be performed according to the sample size, age group, patient severity, treatment duration, and other relevant parameters.

Sensitivity analysis: We will conduct sensitivity analyses by removing each study one at a time to evaluate the stability of the results.

Country(ies) involved: China.

Keywords: knee osteoarthritis; Complementary and alternative medicine; network meta-analysis; randomized controlled trials.

Contributions of each author:
Author 1 - Boyu Wu.
Author 2 - Lei Yang.
Author 3 - Chengwei Fu.
Author 4 - Yantao Guo.