INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Effectiveness and safety of the available treatments for the pain of knee osteoarthritis: a protocol for a systematic review and network meta-analysis

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Review question / Objective: **We aim to access the effectiveness and safety of acupuncture, intra-articular injection and some oral medicine on knee osteoarthritis pain in a network meta-analysis.**
Condition being studied: **We considered randomized control trials (RCTs) of adults with knee osteoarthritis comparing 2 or more of the following: acupuncture, moxibustion, fire needles, sham acupuncture, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, IA placebo, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen), Acetaminophen, duloxetine Hydrochloride and oral placebo.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 February 2021 and was last updated on 06 February 2021 (registration number INPLASY202120022).

INTRODUCTION

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IA placebo, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen), Acetaminophen, duloxetine Hydrochloride and oral placebo.

METHODS

Search strategy: We searched the MEDLINE, EMBASE and Cochrane Register of Controlled Trials from inception through 14 October 2020. The terms included acupuncture, moxibustion, fire needles, sham acupuncture, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, IA placebo, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen), Acetaminophen, duloxetine Hydrochloride and oral placebo.

Participant or population: Studies that enrolled patients with a clinical diagnosis of knee osteoarthritis will be included, and there are no restrictions on gender, age, or ethnicity.

Intervention: We will consider studies evaluating the following treatments: acupuncture (Ear Acupunctures, Electroacupuncture), moxibustion, fire needles, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen) Acetaminophen, and duloxetine Hydrochloride, irrespective of preparations (tablet or capsule), dosage, regimen and length of treatment.

Comparator: Controlled interventions included control groups with no treatment, sham/placebo groups, or other conventional treatments, which act as vital links for the incorporation of indirect evidence in the networks.

Study designs to be included: All randomized controlled trials comparing 2 or more of the following: acupuncture, moxibustion, fire needles, sham acupuncture, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, IA placebo, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen), Acetaminophen, duloxetine Hydrochloride and oral placebo, will be included.

Eligibility criteria: Type of studies All randomized controlled trials comparing 2 or more of the following: acupuncture, moxibustion, fire needles, sham acupuncture, intra-articular (IA) hyaluronic acid, IA corticosteroids, IA glucocorticoids, IA placebo, six different Non-steroidal anti-inflammatory drugs (NSAIDs) (Refecoxib, Lumiracoxib, Diclofenac, Celecoxib, Naproxen, Ibuprofen), Acetaminophen, duloxetine Hydrochloride and oral placebo, will be included. Trials must have randomly assigned, on average, at least 100 patients per group to minimize bias due to small study effects. Non-randomized studies or trials published as abstracts only will be excluded. Type of participants Studies that enrolled patients with a clinical diagnosis of knee osteoarthritis will be included, and there are no restrictions on gender, age, or ethnicity. Type of interventions We will consider studies evaluating the following treatments: acupuncture (Ear Acupunctures, Electroacupuncture), moxibustion, fire needles, intra-articular (IA) hyaluroni.

Information sources: We searched the MEDLINE, EMBASE and Cochrane Register of Controlled Trials from inception through 14 October 2020. Information such as year of publication, number of patients enrolled, participant characteristics, features of interventions in treatment and control groups, types of outcome assessment, methodological quality of primary studies, data analysis approaches, and sources of funding were extracted.

Main outcome(s): Our prespecified primary outcome was pain. Knee pain levels will be assessed by the visual analogue scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score of pain subscale or the WOMAC global scores.

Additional outcome(s): Function measures: the WOMAC score of physical functional or Lysholm knee scoring scale. Quality of life: the short from health survey (SF-36) or the Pittsburgh Sleep Quality of Index (PSQI).

Quality assessment / Risk of bias analysis: Two authors independently assessed the risk of bias of each included study following the Cochrane's risk of bias tool. It will be assessed with methodological quality as low risk, high risk, or unclear risk of bias, which contains 7 specific domains: random sequence generation, allocation concealment, blinding of the subjects and researchers, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Strategy of data synthesis: Firstly, we will conduct classic pair-wise meta-analyses to synthesize studies with the same pair of interventions by using RevMan 5.3 Software. The results will be reported as standard mean differences (SMD) with the corresponding 95% confidence interval (CI). Statistical heterogeneity between studies was assessed by the $\chi 2$ test with a P value of ≤ 0.01 indicating significant heterogeneity. Secondly, the network meta-analyses are conducted using a hierarchical random-effects model within the Bayesian framework. Then, we will perform the Bayesian network meta-analysis for assessing the therapeutic effect among these treatments in KOA using WinBUGS1.4.3 software, which uses Markov chain Monte Carlo (MCMC) simulation methods to run thousands of simulated iterations based on the data and description of the proposed distributions for relevant parameters.

Subgroup analysis: If the necessary data is available, subgroup analyses will be done for the constituents of the OA Kellgren-Lawrence grade such asI, II tolII whether there is a difference in outcomes.

Sensitivity analysis: Sensitivity analyses were conducted to assess the impact of excluding nonrandomized studies and to examine the impact of low methodological quality.

Language: English.

Country(ies) involved: China.

Keywords: knee osteoarthritis, acupuncture, intra-articular injection, NSAIDs, network meta-analysis.

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