INPLASY PROTOCOL

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The authors declare no conflicts of interest.

A comparison of the effects of Acupoint injection combined with Hyaluronic Acid versus isolated Hyaluronic Acid for knee osteoarthritis: Protocol for systematic review and meta-analysis of randomized controlled trials

Zhou, X[1]; Xiang, KM[2]; Yuan, XY[3].

Review question / Objective: **The aim of this review is to evaluate the effectiveness of Acupoint injection combined with Hyaluronic Acid injection compared with isolated Hyaluronic Acid injection for knee osteoarthritis.**

Condition being studied: **Knee osteoarthritis (KOA) is a kind of degenerative osteoarthropathy. A typical knee osteoarthritis patient develops pain from squatting or going up and down stairs in the early stage, which will gradually increase, and in the middle and late stages, it will appear as walking on flat roads or resting. It also produces pain, which seriously affects the quality of life of the patient. Early to mid-stage knee osteoarthritis patients often receive non-steroidal anti-inflammatory drugs(NSAIDs) or intra-articular injection of Hyaluronic Acid(HA). Although HA is no longer recommended in the guidelines of the American Academy of Orthopaedic Surgeons(AAOS), it is due to its exact clinical effect, many surgeons are still using it. Of course, some conservatively treated patients who simply receive HA injections will inevitably not get satisfactory results. Because the pain source of knee osteoarthritis not only comes from the synovial, joint Capsules and subchondral bone in the joint cavity, but also the fascia, ligament and tendon attachment points outside the joint cavity.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 October 2020 and was last updated on 17 October 2020 (registration number INPLASY2020100058).

INTRODUCTION

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METHODS

Search strategy: CNKI, Wanfang, VIP, CBM, PubMed, Embase and Cochrane Library databases were searched for this study. Take the subject terms combined with free words to search, take PubMed as an example: terms consist of disease (osteoarthritis, knee OR knee osteo-arthritis OR knee osteoarthritides OR Osteoarthritis of Knee OR Osteoarthritis of the Knee) and intervention (Acupoint Injection OR Acupuncture Point Injection OR point injection therapy OR Acupuncture Points)and Comparison (Sodium Hyaluronate OR Hyaluronic acid) and research types (randomized controlled trial OR controlled clinical trial OR random trials).

Participant or population: Patients were diagnosed with knee osteoarthritis and the study belongs to randomized controlled trial.Clinical results included Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores, Lequesne index score, Lysholm score,Japanese Orthopaedic Association(JOA) score, clinical effectiveness and Visual analog scale (VAS). Experimental group must cover Acupoint injection combined with Hyaluronic Acid(HA) injection and control group must cover intra-articular injection with Hyaluronic Acid(HA). Otherwise, studies will be excluded if they cannot meet the inclusion criteria.

Intervention: Intervention of the experimental group must cover Acupoint injection combined with Hyaluronic Acid(HA) injection. There are no restrictions on the way of dosage and treatment period.

Comparator: The control group must cover intra-articular injection with Hyaluronic Acid(HA).

Study designs to be included: Only randomized controlled trials will be included in this study.

Eligibility criteria: Randomized clinical trials will be included irrespective of blinding, publication status or language.

Information sources: We will search articles in seven electronic database including:CNKI, Wanfang, VIP, CBM, PubMed, Embase and Cochrane Library databases. All the publications, with no time restrictions, will be searched without any restriction of countries or article type. Reference list of all selected articles will independently screened to identify additional studies left out in the initial sea.

Main outcome(s): The primary outcome is Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores.

Additional outcome(s): The secondary outcome are clinical effectiveness, Lequesne index score,Lysholm score, Japanese Orthopaedic Association(JOA) score,Visual analog scale (VAS) and the incidence of adverse reaction.

Data management: (1)NoteExpress and Excel software will be used to extract data, and the content will be stored in electronic chart. (2)Different researchers will separately screen the titles and abstracts of records acquiaed potential eligibility which comes from the electronic databases. Full texts screening and data extraction will be conducted afterwards independently. Any disagreement will be resolved by discussion until consensus is reached or by consulting a third author.In this step, we will use NoteExpress. (3)The following data will be extracted: author, year of publication, country, interventions of experimental groups and control groups, time point, outcome measures, age of patients, total number of people included in the study, patients' basic information, etc. Different researchers will separately extract data. Any disagreement regarding data extraction will be will be resolved by discussion until consensus is reached or by consulting a third author. In this step, we will use Excel.

Quality assessment / Risk of bias analysis: Two reviewers will independently assesses the quality of the selected studies according to the Cochrane Collaboration's tool for randomized controlled trials.Items will be evaluated in three categories:Low risk of bias, unclear bias and high risk of bias.The following characteristics will be evaluated: random sequence generation (selection Bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data(attrition bias), selective reporting(reporting bias)and other biases. Results from these questions will be graphed and assessed using Review Manager 5.4. The results will be presented in the form of a graph, and will be independently evaluated by two researchers.If there are differences of opinion, they will be discussed with the third researcher.

Strategy of data synthesis: Statistical analysis will be conducted using RevMan 5.4 software. For continuous data, will be used mean difference (MD) as the effect indicator with 95% confidence interval, and dichotomous data will be calculated as risk ratio (RR) or odds ratio (OR)as the effect index with 95% confidence interval.If the studies with no statistical homogeneity, the fixed-effect model can be used for analysis; if the studies with significant statistical heterogeneity, random effects model analysis will be used.

Subgroup analysis: We will consider subgroups analysis intervention of the experimental group.

Sensibility analysis: Through sensitivity analysis assess the source of heterogeneity, by excluding low-quality studies, or by excluding one of the included studies in turn, if there is no significant change in the heterogeneity, the results are robust, otherwise, the excluded study is heterogeneous originate.

Language: No restriction on language.

Country(ies) involved: China.

Keywords: systematic review; protocol; Acupoint injection;Hyaluronic Acid; knee osteoarthritis; randomized controlled trial

Dissemination plans: We plan to publish a systematic review based on this protocol.

Contributions of each author:
Author 1 - Zhou Xing - Drafted and improved the manuscript.
Author 2 - Xiang Ke-meng - Revise this protocol; search strategy; analysis of results.
Author 3 - Yuan Xiang-yao - data collection.