

INPLASY PROTOCOL

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None declared.

Effect of acupuncture-related therapy in rodent animal models efficacy and immune-inflammatory response of knee osteoarthritis a systematic review and Network Meta-analysis

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Review question / Objective: Is the therapeutic effect of acupuncture-related therapies satisfactory for rodent animal models of KOA? What are the mechanisms of action involved?

Condition being studied: Knee osteoarthritis (KOA) is a chronic degenerative disease affecting the elderly worldwide and characterized by osteophyte generation and cartilage loss on the surface of the knee joint, which leads to limited knee movement, stiffness, dysfunction, and affects the quality of life of patients. Globally, the incidence of KOA has increased significantly and younger, from which it is imperative to find more scientific and effective treatments for KOA. At present, there are shortcomings in the treatment of KOA. The therapeutic targeting of oral non-steroidal anti-inflammatory medicine is not high, and its tolerance and safety remain to be solved. Joint replacement and other surgeries are effective methods for the treatment of patients with advanced diseases, but surgical treatment is not only costly, but also has surgical risks and loosening. Many patients with KOA have not reached advanced surgical indications, so it is necessary to find effective non-surgical therapies. Meanwhile, some studies suggest that for patients with KOA, acupuncture therapies can significantly reduce pain intensity, improve functional mobility and quality of life, and have been widely used in clinical practice. Therefore, acupuncture is considered as an effective comprehensive treatment for KOA. However, the evidence supporting the application of acupuncture therapies to KOA is still insufficient, and it is yet unclear what immune and inflammatory mechanisms are involved.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 November 2022 and was last updated on 29 November 2022 (registration number INPLASY2022110152).

INTRODUCTION

Review question / Objective: Is the therapeutic effect of acupuncture-related

therapies satisfactory for rodent animal models of KOA? What are the mechanisms of action involved?

Rationale: Knee osteoarthritis (KOA) is a common degenerative disease that affects the quality of life of patients, with a significant increase in the incidence and a tendency to be younger, but there are limitations in the currently available treatments. Acupuncture has already been suggested to be applied for KOA through immune reduction of inflammation and modulation of cytokines. However, no network Meta-analysis has been performed to analyze the effect of acupuncture on animal models of KOA. Therefore, this study will be the first attempt to systematically evaluate the effectiveness of acupuncture-related therapies in the treatment of KOA, and to explore the immune-inflammation mechanism involved.

Condition being studied: Knee osteoarthritis (KOA) is a chronic degenerative disease affecting the elderly worldwide and characterized by osteophyte generation and cartilage loss on the surface of the knee joint, which leads to limited knee movement, stiffness, dysfunction, and affects the quality of life of patients. Globally, the incidence of KOA has increased significantly and younger, from which it is imperative to find more scientific and effective treatments for KOA. At present, there are shortcomings in the treatment of KOA. The therapeutic targeting of oral non-steroidal anti-inflammatory medicine is not high, and its tolerance and safety remain to be solved. Joint replacement and other surgeries are effective methods for the treatment of patients with advanced diseases, but surgical treatment is not only costly, but also has surgical risks and loosening. Many patients with KOA have not reached advanced surgical indications, so it is necessary to find effective non-surgical therapies.

Meanwhile, some studies suggest that for patients with KOA, acupuncture therapies can significantly reduce pain intensity, improve functional mobility and quality of life, and have been widely used in clinical practice. Therefore, acupuncture is considered as an effective comprehensive treatment for KOA. However, the evidence supporting the application of acupuncture

therapies to KOA is still insufficient, and it is yet unclear what immune and inflammatory mechanisms are involved.

METHODS

Search strategy: Web of science, PubMed, Embase, CBM, China Knowledge Network (CNKI), WanFang and VIP Database will be searched. Search terms will include: "Acupuncture", "Acupuncture Therapy", "Manual acupuncture", "Electro-acupuncture", "Internal heat needle", "acupotomy", "Needle knife", "Warming needle", "Warm acupuncture", "Knee Osteoarthritis", "Knee Osteoarthritis", "Osteoarthritis of Knee", "Osteoarthritis of the Knee", "Animal Experimentation", "Animal", "Animal Experimentation", "Animal Research", "Research, Animal", "Animal Experimental Use", "Animal Experimental Uses", "Experimental Use, Animal", "Experimental Uses", "Animal Experiments", "Animal Experiment", "Experiment, Animal", "Experiments, Animal". Articles published between database establishment and October 2022 will be sought. What's more, we will search for articles in English or Chinese. The searches will be re-run just before the final analyses and further studies retrieved for inclusion.

Participant or population: Rodents with KOA model will be studied, no matter what modeling methods are adapted.

Intervention: Acupuncture-related therapies (e.g. Manual acupuncture, electro-acupuncture, warm acupuncture, acupotomy, etc) will be studied.

Comparator: The control groups are planned to include: the normal group without any operations or treatments, KOA model group without treatments, sham operation group without KOA modeling or treatments, and medicine group with non-Chinese herbal drug therapies. Any acupuncture-related therapies will be excluded.

Study designs to be included: Randomized controlled animal experiments will be

studied. The followings will be excluded:
1) Non-randomized controlled or.

Eligibility criteria: Studies without original data or incomplete data that can not be analyzed will be excluded.

Information sources: Electronic databases including Web of science, PubMed, Embase, CBM, China Knowledge Network (CNKI), WanFang and VIP Database will be searched. When primary data are missing, we will try to contact the authors by mail or telephone, so as to obtain the primary data that are not identified but are of importance to the review.

Main outcome(s): 1) IL-1 β (no/ml). It is a continuous variable which will be presented as mean square error (SMD) and its 95% confidence interval (CI); 2) TNF- α (no/ml). It is a continuous variable which will be presented as mean square error (SMD) and its 95% confidence interval (CI).

Additional outcome(s): 1) MMP-3 (no/ml); 2) MMP-13 (no/ml); 3) Lequesne index scale (point(s)); 4) Mankin score (point(s)). Since the outcomes above are all continuous variables, they will be presented as mean square error (SMD) and the 95% confidence interval (CI).

Data management: Two investigators (YJH and HH) will independently extract the data from the texts and conduct a cross-check. Disagreements were resolved by discussion or consultation with a third party (QQC). When primary data are missing or presented graphically in the included studies, we will try to contact the authors by mail or telephone, so as to obtain the primary data that are not identified but are of importance to the review. If the author fails to reply, the values in the figure will be scanned by GetData Graph Digitizer 2.26 software.

Quality assessment / Risk of bias analysis: According to SYRCLE 's "Risk of Bias Evaluation" tool, the quality assessment risk of bias was performed in 10 aspects of the entered articles using the judgment words "high risk", "low risk", and "unclear

risk", including: (1) sequential generation (selective bias); (2) baseline characteristics (selective bias); (3) allocation concealment (selective bias); (4) random housing (performance bias); (5) blinding (performance bias); (6) random outcome assessment (detection bias); (7) blinding (detection bias); (8) incomplete data reporting (reporting bias); (9) selective outcome reporting (reporting bias); (10) other sources of bias (other). For each included article, the above 10 items were judged as low bias, high bias and unclear bias (lack of relevant information or uncertain bias). Methodological quality evaluation was performed independently by two reviewers (YJH and HH), and agreement was reached according to the third party (QQC) opinion if there was disagreement between the two reviewers.

Strategy of data synthesis: Since all outcomes (Lequesne index scale, Mankin score, IL-1 β , TNF- α , MMP3, MMP13) included are measurement data, quantitative syntheses will be conducted for all outcome measure. Stata15.0 will be used to perform Meta-analysis as well as network Meta-analysis between groups. Heterogeneity among studies will be tested with I^2 . If $I^2 \leq 50\%$, it indicates that there may be little possibility of a high heterogeneity among studies, then a fixed-effect model will be used for the outcome measure; otherwise the heterogeneity may tend to be obvious, which means that a random-effects model for the outcome measure.

Statistical analysis and graphical drawing will be performed using Stata15.0 software. For network meta-analysis, the method of node segmentation model will be used to judge whether direct and indirect comparisons are consistent. The consistency model or the inconsistency model is planned to be used to indicate the consistency or the inconsistency between direct and indirect comparisons among interventions. What's more, the cumulative ranking probabilities for the interventions will be calculated with the method of SUCRA.

Subgroup analysis: Subgroup analyses will be performed for Lequesne index scale and Mankin score. Considering there may be differences in acupuncture methods in test groups, and differences in treatment courses in both test groups and control groups, subgroup analyses may be performed depending on the specific conditions. Stata15.0 will be used for subgroup analyses.

Sensitivity analysis: Sensitivity analyses will be performed if high heterogeneity among Meta analyses is indicated by I^2 . Sensitivity analyses will help detect the reasons of high heterogeneity and assess the stability of the Meta results.

Language restriction: We plan to search for articles in English or Chinese.

Country(ies) involved: China.

Keywords: Acupuncture; acupotomy; knee osteoarthritis; animal experiment; immunity; inflammation; systematic review; network meta-analysis.

Contributions of each author:

Author 1 - Yingjie Huang - Author 1 and author 2 conceptualized this study. Both of them will design the analysis scheme for data synthesis, and will contribute to the draft of the manuscript. All authors will contribute to the article and approve the submitted version.

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