INPLASY PROTOCOL

To cite: Ye et al. Effects of acupuncture on cartilage p38MAPK and mitochondrial pathways in animal model of knee osteoarthritis: a systematic evaluation and Meta-analysis. Inplasy protocol 202290125. doi: 10.37766/inplasy2022.9.0125

Received: 29 September 2022

Published: 29 September 2022

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Support: **NSFC.No.81704152 and No.82004497**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Effects of acupuncture on cartilage p38MAPK and mitochondrial pathways in animal model of knee osteoarthritis: a systematic evaluation and Meta-analysis

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Review question / Objective: **Participants: Animals with knee osteoarthritis established by various methods. Intervention: Receiving acupuncture treatment after modeling. Comparison: Untreated animal models of knee osteoarthritis (model group). Results: cytokines of the p38MAPK and mitochondrial pathway in cartilage tissue (including P38MAPK, IL-1β, TNF-α, P-P38MAPK, MMP-13, MMP-1, ADAMST-5, collagen II, aggrecan, Bax mRNA, Bcl-2 mRNA Caspase-3 mRNA, Caspase-9 mRNA, Bax, Bcl-2, caspase-3, Caspase-9, Cyt-c); (2) secondary outcome indicators: chondrocyte apoptosis rate, Mankin's score measuring the extent of cartilage damage and cartilage morphometric score (including BV/TV, Tb.Th, Tb.N , Tb.sp).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 September 2022 and was last updated on 12 November 2022 (registration number INPLASY202290125).

INTRODUCTION

Review question / Objective: **Participants: Animals with knee osteoarthritis established by various methods. Intervention: Receiving acupuncture treatment after modeling. Comparison: Untreated animal models of knee osteoarthritis (model group). Results: cytokines of the p38MAPK and mitochondrial pathway in cartilage tissue (including P38MAPK, IL-1β, TNF-α, P-P38MAPK, MMP-13, MMP-1, ADAMST-5, collagen II, aggrecan, Bax mRNA, Bcl-2 mRNA Caspase-3 mRNA, Caspase-9 mRNA, Bax, Bcl-2, caspase-3, Caspase-9,**

Cyt-c); (2) secondary outcome indicators: chondrocyte apoptosis rate, Mankin's score measuring the extent of cartilage damage and cartilage morphometric score (including BV/TV, Tb.Th, Tb.N , Tb.sp).

Condition being studied: In order to improve the accuracy of clinical research and master the internal mechanism of acupuncture in the treatment of knee osteoarthritis, the research of animal model of acupuncture in the treatment of knee osteoarthritis came into being. It is well known that the main pathological change of knee osteoarthritis is cartilage degeneration. After the occurrence of knee osteoarthritis, the balance between synthesis and metabolism of chondrocytes is broken, which leads to the limited secretion of extracellular matrix to maintain normal cartilage function, and finally accelerates the occurrence of cartilage destruction. We know that acupuncture can improve the apoptotic state and degree of destruction of cartilage by regulating the level of cytokines in cartilage. Therefore, it has become a major trend to study the regulation of cartilage by acupuncture and moxibustion in animal models of knee osteoarthritis.

METHODS

Participant or population: Animals with knee osteoarthritis established by various methods are not limited in species, sex, weight and age.

Intervention: Acupuncture treatment should be carried out after the model is established, with no restrictions on acupuncture methods, types, frequency, course of treatment and stimulation intensity.

Comparator: Knee osteoarthritis model group animals without intervention.

Study designs to be included: This study included animal studies of acupuncture in the treatment of knee osteoarthritis, focusing on the mechanism of effects at the cartilage level.

Eligibility criteria: We developed the following inclusion and exclusion criteria for this study in strict accordance with the PICOS (Participation, Intervention, Comparison, Outcome, Type of Study) principles. Participant type (P): all studies on animals with KOA were included, without restriction on species, sex, month of age, or modeling method, provided that the sent samples were cartilaginous tissue. Non-animal, non-chondrogenic level studies of KOA were excluded. Intervention type (I): In the treatment of KOA, the intervention group was treated with acupuncture, with no restrictions on method, duration, time, or acupuncture points. If different electro-acupuncture frequencies or different intervention sessions existed, the highest frequency or the longest intervention duration was selected for analysis. Studies in which non-acupuncture or acupuncture was not the primary intervention were excluded. Comparison type (C): the model group was modeled only without any interventions. Outcome type (O): (1) Main outcome indicators: cytokines of the p38MAPK and mitochondrial pathway in cartilage tissue (including P38MAPK, IL-1β, TNF-α, P-P38MAPK, MMP-13, MMP-1, ADAMST-5, collagen II, aggrecan, Bax mRNA, Bcl-2 mRNA Caspase-3 mRNA, Caspase-9 mRNA, Bax, Bcl-2, caspase-3, Caspase-9, Cyt-c); (2) secondary outcome indicators: chondrocyte apoptosis rate, Mankin's score measuring the extent of cartilage damage and cartilage morphometric score (including BV/TV, Tb.Th, Tb.N , Tb.sp). Study type(s): all randomized controlled studies investigating the cartilage dimension of acupuncture intervention in KOA animal models were included. All clinical case reports, reviews or conferences were excluded. No language was restricted to ensure the most complete studies could be included.

Information sources: This meta-analysis was conducted according to the PRISMA 2020 statement: an updated guidelines for reporting systematic reviews. This review does not have any preregistered protocols. two authors independently searched the

databases of Pubmed、Embase、 Web of science(including Medline)、cochrane library、Scopus、CNKI、Wan Fang、VIP. The search time is limited to the establishment of the database until September 2022. The search terms are:acupuncture, electroacupuncture, acupoint, Osteoarthritis, Knee, Knee Osteoarthritides, Knee Osteoarthritis, Animal Model, animals. each search Word are used alone or in combination.

Main outcome(s): cytokines of the p38MAPK and mitochondrial pathway in cartilage tissue (including P38MAPK, IL-1β, TNF-α, P-P38MAPK, MMP-13, MMP-1, ADAMST-5, collagen II, aggrecan, Bax mRNA, Bcl-2 mRNA Caspase-3 mRNA, Caspase-9 mRNA, Bax, Bcl-2, caspase-3, Caspase-9, Cyt-c).

Additional outcome(s): chondrocyte apoptosis rate, Mankin's score measuring the extent of cartilage damage and cartilage morphometric score (including BV/TV, Tb.Th, Tb.N , Tb.sp).

Quality assessment / Risk of bias analysis: The methodological quality of each included study was assessed by two authors using a 10-item checklist modified from the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) checklist: Sample size calculation; A statement describing temperature and humidity control; Randomization to treatment or control; Use a reasonable knee osteoarthritis model; Assess the success of the model; The use of anesthetics with no obvious specificity; Results Blind method; Comply with animal ethics regulations; Published in a peer-reviewed journal; Declare no potential conflicts of interest. The sum of the quality scores was recorded for each article, with a possible total score of 10 points.

Strategy of data synthesis: Review Manager 5.4 was used for statistical analysis of the data . First, the heterogeneity test was performed. When the studies were homogenous ($P \geq 0.05$, $I2 \leq 50\%$), the fixed-effects model (FE) was used for analysis. If there was significant heterogeneity among the studies ($P < 0.05$, $I2 > 50\%$), a random-effects model (RE) was used for the analysis,and a sensitivity analysis was performed to examine the sources of heterogeneity and to assess the stability of the results. The outcome indicators of this study were all continuous variables, and their outcomes were expressed by standard mean difference (SMD) and 95% confidence interval (95% CI). The 95% CI did not contain 0, indicating that the results were statistically different ($P < 0.05$), and finally a funnel plot was used to analyze potential publication bias.

Subgroup analysis: We will conduct a subgroup analysis of studies with high heterogeneity and will consider the stability of acupuncture effects and look for sources of heterogeneity at the levels of different acupuncture modalities, different species selection, and different gender distribution.

Sensitivity analysis: If random-effects model (RE) was used for the analysis, and a sensitivity analysis was performed to examine the sources of heterogeneity and to assess the stability of the results.

Country(ies) involved: China.

Keywords: Knee osteoarthritis, acupuncture, animal models, pathways, cytokines, Meta-analysis.

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