

INPLASY PROTOCOL

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Review Stage at time of this submission: Piloting of the study selection process.

Conflicts of interest:
None.

Clinical efficacy and safety of different sources of mesenchymal stem cells in the treatment of knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: The aim of this meta-analysis of randomized controlled trials is to compare the clinical efficacy and safety of different sources of mesenchymal stem cells (MSCs) for the treatment of knee osteoarthritis (OA).

Condition being studied: With the aging of the world's population, the prevalence of osteoarthritis (OA) has been increasing in recent years. In Asia, it has been estimated that people aged 65 years and over will more than double in the next two decades, from 6.8% in 2008 to 16.2% in 2040. Knee OA has been one of the leading causes of global disability. The typical pathological characteristic is cartilage destruction, inflammation, remodeling of sub-articular bone, osteophyte formation, which can eventually lead to irreversible damage to the articular cartilage. Mesenchymal stem cells (MSCs) are a heterogeneous subset of stromal stem cells that can be isolated from many adult tissues. They can inhibit the release of pro-inflammatory cytokines and promote the survival of damaged cells. There is still a lack of clinical evaluation of MSCs from different differentiation sources in the treatment of KOA. Thus, we intended to perform a meta-analysis to assess the clinical efficacy and safety of various sources of mesenchymal stem cells in the treatment of knee osteoarthritis.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 June 2020 and was last updated on 25 June 2020 (registration number INPLASY202060096).

INTRODUCTION

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METHODS

Participant or population: Patients with knee osteoarthritis.

Intervention: Mesenchymal stem cells(MSCs) injection was the main intervention.

Comparator: In different studies, the control group included hyaluronic acid, only arthroscopic debridement, PRP, placebo, conservative management, saline, a corticosteroid.

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

Eligibility criteria: The study protocol will be developed and executed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. All of the following inclusion criteria in the PICOS order will be met by the studies included in our meta-analysis: (1) population: patients with knee osteoarthritis; (2) intervention: Mesenchymal stem cells(MSCs) injection was the main intervention; (3) comparison intervention: In different studies, the

control group included hyaluronic acid, only arthroscopic debridement, PRP, placebo, conservative management, saline, a corticosteroid; (4) outcome measures: mean changes in The visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), The Knee Injury and Osteoarthritis Outcome Score (KOOS), and cumulative assessment of pain scores and function scores (5) study design: RCTs. The research data were complete and sufficient. Animal experiments and in vitro studies were excluded. Besides, case reports, meeting abstracts, review studies, not included knee with osteoarthritis, insufficient data researches, and education without appropriate control arm were excluded. Two independent reviewers will screen the titles and abstracts of the potentially relevant studies to determine their eligibility based on the criteria. Disagreements will be resolved through a discussion with a third reviewer.

Information sources: PubMed, EMBASE, Cochrane Library, Web of Science, Sinomed, CNKI, Cqvip, the WanFang Database.

Main outcome(s): Mean changes in The visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), The Knee Injury and Osteoarthritis Outcome Score (KOOS), and cumulative assessment of pain scores and function scores.

Additional outcome(s): International Knee Documentation Committee (IKDC), American knee society knee score (AKS), Lequesne algofunctional indices (Lequesne), and Lysholm knee scale (Lysholm).

Quality assessment / Risk of bias analysis: The risk of bias assessment will be completed by two reviewers, respectively. Using Cochrane Collaboration's risk of bias tool. Funnel plots and Egger's tests provide an effect on the likely presence of bias in meta-analyses. Both of the above two methods could be used to evaluate publication bias(Stata version 14.0,

Corporation, USA). When there was a disagreement in the evaluation process, it was resolved through consensus between two reviewers or through consultation with the third reviewers.

Strategy of data synthesis: We made a comparative analysis between the experimental groups and the control groups treated with Review Manager Version 5.3 (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The heterogeneity of statistical data was evaluated by I^2 . When $I^2 > 50\%$, it was proved to have a high level of heterogeneity. Because the included studies were assumed to be random samples of all possible studies, with intra-studies sampling differences and inter-studies variations, the uncertainty of the results was estimated using a random-effects model. The outcome pooled estimate of effect, and the overall summary effect of each study was shown in the Forest plots. In the 95% confidence intervals(CIs), the MSCs treatment effects were reflected by the mean differences(MDs). In all analyses, $P < 0.05$ was considered to be statistically significant. The P values of all reports come from the two-sided version of the respective test.

Subgroup analysis: The difference in VAS and WOMAC was defined as the mean changes of bone marrow-derived, adipose-derived, and umbilical cord-derived mesenchymal stem cells from baseline to the outcome. In terms of pain comprehensive evaluation, we adopt VAS and KOOS - pain scales to analyze. In terms of function comprehensive evaluation, we adopt Lysholm and KOOS - ADL scales to analyze. In AKS and IKDC scales, we adopt different follow-up times for subgroup analysis.

Sensibility analysis: Sensitivity analyses will be undertaken to determine the potential source of heterogeneity when significant.

Language: No language limitation.

Country(ies) involved: China.

Other relevant information: None.

Keywords: mesenchymal stem cells, knee osteoarthritis, meta-analysis, RCTs.

Dissemination plans: None.

Contributions of each author:

Author 1 - Weijie Yu - Weijie Yu conceived the study, designed the review, and wrote the initial manuscript.

Author 2 - Aifeng Liu - Aifeng Liu , The general head of research, supervised the whole system evaluation process, was responsible for all contact with the editorial department, and received consultation from readers.

Author 3 - Jixin Chen - Jixin Chen participated in literature screening, data extraction and bias risk assessment.

Author 4 - Ao Wu - Ao Wu participated in literature screening, data extraction, and bias risk assessment.

Author 5 - Yongda Wu - Yongda Wu participated in literature screening, data extraction, and bias risk assessment.