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Comparative Effectiveness and Safety of Non-Surgical Interventions for Moderate-to-Severe Knee Osteoarthritis: A Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - 2020022.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 January 2026 and was last updated on 26 January 2026.

INTRODUCTION

Review question / Objective The objective of this systematic review and network meta-analysis is to compare the effectiveness and safety of various non-surgical interventions for moderate to severe knee osteoarthritis. Specifically, we aim to:
Evaluate and compare the efficacy of different intra-articular injections (including platelet-rich plasma [PRP], hyaluronic acid [HA], corticosteroids, mesenchymal stem cells [MSCs], and other biological therapies) in reducing pain and improving function in patients with moderate to severe knee osteoarthritis.
Assess the short-term and long-term outcomes using validated outcome measures including Visual Analogue Scale (VAS) for pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) for pain, stiffness, and physical function.
Compare the safety profiles of different interventions by analyzing adverse events.
Provide a ranking of interventions based on their comparative effectiveness to guide clinical decision-making.

Condition being studied Knee Osteoarthritis (KOA) Knee osteoarthritis is a degenerative joint disease characterized by progressive cartilage degradation, subchondral bone changes, osteophyte formation, and synovial inflammation. It is one of the most common musculoskeletal disorders, particularly affecting middle-aged and elderly populations. Patients typically present with knee pain, stiffness, reduced range of motion, and functional impairment, which significantly impact quality of life. The severity of knee osteoarthritis is commonly assessed using the Kellgren-Lawrence (K-L) grading system, with moderate to severe cases (K-L grades 2-4) often requiring various non-surgical interventions to manage symptoms and improve function.

METHODS

Participant or population Inclusion Criteria:
Adults (≥18 years old) diagnosed with knee osteoarthritis according to clinical and/or radiographic criteria (e.g., American College of Rheumatology [ACR] criteria)
Patients with moderate to severe knee osteoarthritis, defined as Kellgren-Lawrence (K-L) grade 2-4 on radiographic assessment
Patients presenting with knee pain and/or functional impairment
No restriction on sex, race, or nationality
Exclusion Criteria:
Patients with inflammatory arthritis (e.g., rheumatoid arthritis, gout, psoriatic arthritis)
Patients with previous knee arthroplasty or other major knee surgery
Patients with active infection in or around the knee joint
Patients with severe systemic diseases that may affect treatment outcomes
Patients with K-L grade 0-1 (mild or no osteoarthritis).

Intervention The interventions of interest include various non-surgical treatments for moderate to severe knee osteoarthritis, primarily focusing on intra-articular injections:
1. Platelet-Rich Plasma (PRP)
Autologous platelet-rich plasma injections
Including leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP)
Platelet-rich growth factors (PRGF)
2. Hyaluronic Acid (HA)
Viscosupplementation with hyaluronic acid
Including different molecular weights (low, medium, high)
Various commercial preparations (e.g., Hylan G-F 20, EUFLEXXA)
3. Mesenchymal Stem Cells (MSCs)
Bone marrow-derived mesenchymal stem cells (BM-MSCs)
Adipose-derived mesenchymal stem cells (AD-MSCs)
Autologous or allogeneic stem cell preparations
4. Corticosteroids
Intra-articular corticosteroid injections (e.g., triamcinolone, methylprednisolone)
5. Other Biological Therapies
Autologous conditioned plasma (ACP)
Low molecular weight fraction of 5% human serum albumin (LMWF-5A)
Other regenerative medicine approaches
6. Placebo/Control
Saline injections
Sham procedures.

Comparator In this network meta-analysis, each intervention will be compared against all other interventions within the network. The comparators include:
1. Active Comparators:
Platelet-rich plasma (PRP)
Hyaluronic acid (HA)
Mesenchymal stem cells (MSCs)
Corticosteroids
Other biological therapies (e.g., PRGF, ACP)
2. Control Comparators:
Placebo (saline injection)
Sham procedure
No treatment / usual care
Network Structure:
All included interventions will form a connected network, allowing both direct comparisons (from head-to-head trials) and indirect comparisons (through common comparators) to estimate the relative effectiveness and safety of each intervention.

Study designs to be included RCT.

Eligibility criteria
Inclusion Criteria:
1. Study Design:
Randomized controlled trials (RCTs)
Published in peer-reviewed journals
No language restrictions
2. Participants:
Adults (≥18 years old) with diagnosed knee osteoarthritis
Moderate to severe knee osteoarthritis (Kellgren-Lawrence grade 2-4)
No restrictions on sex, race, or nationality
3. Interventions:
Intra-articular injections including: platelet-rich plasma (PRP), hyaluronic acid (HA), mesenchymal stem cells (MSCs), corticosteroids, or other biological therapies
At least two different interventions compared
4. Comparators:
Any of the above interventions, placebo (saline), sham procedure, or no treatment
5. Outcomes:
Studies must report at least one of the following outcomes: VAS (Visual Analogue Scale) for pain, WOMAC (Western Ontario and McMaster Universities Arthritis Index), or adverse events
Exclusion Criteria:
1. Study Design:
Non-randomized studies, observational studies, case reports, case series, reviews, editorials, and conference abstracts without full-text availability
2. Participants:

Studies including patients with inflammatory arthritis (rheumatoid arthritis, gout, psoriatic arthritis)
Studies including patients with previous knee arthroplasty
Studies focusing on mild osteoarthritis (K-L grade 0-1) only
3. Interventions:
Studies evaluating surgical interventions only
Studies without clear description of intervention protocols
4. Outcomes:
Studies not reporting VAS or WOMAC outcomes
Studies with insufficient data for meta-analysis.

Information sources Electronic Databases:

The following electronic databases will be systematically searched from inception to the present:
PubMed/MEDLINE - National Library of Medicine
Embase - Elsevier
Cochrane Central Register of Controlled Trials (CENTRAL) - Cochrane Library
Web of Science - Clarivate Analytics
Scopus - Elsevier
CNKI (China National Knowledge Infrastructure) - Chinese database
Wanfang Database - Chinese database
VIP Database - Chinese database
Clinical Trial Registries:
ClinicalTrials.gov (https://clinicaltrials.gov)
WHO International Clinical Trials Registry Platform (ICTRP)
Chinese Clinical Trial Registry (ChiCTR)
Grey Literature:
OpenGrey
ProQuest Dissertations & Theses
Conference proceedings from relevant orthopedic and rheumatology meetings
Manual Search:
Reference lists of included studies and relevant systematic reviews
Citation tracking of key articles
Contact with experts in the field for unpublished data if necessary.

Main outcome(s)

Primary Outcomes:
1. Pain Assessment - Visual Analogue Scale (VAS)
VAS score for knee pain (0-100 mm or 0-10 scale)
Measured at baseline and follow-up time points
Reported as mean change from baseline with standard deviation (SD)
Lower scores indicate less pain (better outcome)
2. Functional Assessment - Western Ontario and McMaster Universities Arthritis Index (WOMAC)
WOMAC total score and subscale scores:
Pain subscale (5 items, 0-20 or 0-50 or 0-500)
Stiffness subscale (2 items, 0-8 or 0-20 or 0-200)
Physical function subscale (17 items, 0-68 or 0-170 or 0-1700)
Measured at baseline and follow-up time points
Reported as mean change from baseline with standard deviation (SD)
Lower scores indicate better function (better outcome)
Measures of Effect:
Continuous outcomes: Mean difference (MD) or Standardized mean difference (SMD) with 95% confidence intervals (CI)
Network meta-analysis will provide surface under the cumulative ranking curve (SUCRA) values to rank interventions.

Quality assessment / Risk of bias analysis

Cochrane tools.

Strategy of data synthesis

1. Pairwise Meta-Analysis:
Traditional pairwise meta-analyses will be conducted for direct comparisons between interventions
Random-effects model will be used to account for heterogeneity across studies
Effect sizes will be expressed as mean difference (MD) for outcomes measured on the same scale, or standardized mean difference (SMD) for outcomes measured on different scales, with 95% confidence intervals (CI)
2. Network Meta-Analysis (NMA):
A Bayesian network meta-analysis will be performed using a random-effects model
Both direct and indirect evidence will be synthesized to estimate relative treatment effects
Network geometry will be presented graphically, with nodes representing interventions and edges representing direct comparisons
Surface under the cumulative ranking curve (SUCRA) values will be calculated to rank interventions by effectiveness
League tables will be generated to present all pairwise comparisons
3. Assessment of Heterogeneity:
Statistical heterogeneity will be assessed using the I^2 statistic and Cochran's Q test
I^2 values of 25%, 50%, and 75% will be considered as low, moderate, and high heterogeneity, respectively
Sources of heterogeneity will be explored through subgroup analyses and meta-regression if sufficient data are available
4. Assessment of Transitivity and Consistency:
Transitivity assumption will be evaluated by comparing the distribution of potential effect modifiers across comparisons

Consistency between direct and indirect evidence will be assessed using node-splitting method
Global inconsistency will be evaluated using the design-by-treatment interaction model
5. Subgroup and Sensitivity Analyses:
Subgroup analyses will be conducted based on: OA severity (K-L grade), follow-up duration, intervention dosage/frequency, and study quality
Sensitivity analyses will be performed by excluding studies with high risk of bias
6. Publication Bias:
Publication bias will be assessed using comparison-adjusted funnel plots
Egger's test will be performed if ≥10 studies are included in a comparison
7. Software:
Statistical analyses will be performed using R software (gemtc, netmeta packages) and/or Stata (network suite).

Subgroup analysis Subgroup analyses will be performed to explore potential sources of heterogeneity and to assess whether treatment effects differ across patient subgroups. The following subgroup analyses are planned:
1. Osteoarthritis Severity:
Moderate OA (Kellgren-Lawrence grade 2-3)
Severe OA (Kellgren-Lawrence grade 3-4)
2. Follow-up Duration:
Short-term follow-up (≤3 months)
Medium-term follow-up (3-6 months)
Long-term follow-up (>6 months or ≥12 months)
3. Patient Age:
Younger patients (<60 years)
Older patients (≥60 years)
4. Baseline Pain Severity:
Mild to moderate baseline pain (VAS <50 mm)
Severe baseline pain (VAS ≥50 mm)
5. Intervention-Specific Subgroups:
PRP preparation type: Leukocyte-rich PRP (LR-PRP) vs. Leukocyte-poor PRP (LP-PRP)
Hyaluronic acid molecular weight: Low vs. Medium vs. High
Stem cell source: Bone marrow-derived vs. Adipose-derived
Stem cell type: Autologous vs. Allogeneic
Number of injections: Single injection vs. Multiple injections
6. Study Quality:
Low risk of bias studies
High risk of bias studies
7. Geographic Region:
Asian studies
Western studies (Europe/North America)
Note: Subgroup analyses will only be conducted if there are sufficient studies (≥3 studies per subgroup) to ensure meaningful comparisons.

Sensitivity analysis Sensitivity analyses will be conducted to assess the robustness of the primary findings and to evaluate the impact of methodological decisions on the results. The following sensitivity analyses are planned:
1. Risk of Bias:
Excluding studies with high overall risk of bias
Including only studies with low risk of bias in key domains (randomization, blinding, incomplete outcome data)
2. Study Design:
Restricting analysis to double-blind randomized controlled trials only
Excluding open-label or single-blind studies
3. Sample Size:
Excluding small studies (sample size 20%)
6. Follow-up Time Points:
Restricting analysis to specific follow-up time points (e.g., 6 months, 12 months)
Excluding studies with very short follow-up (<1 month)
7. Outlier Studies:
Excluding studies with extreme effect sizes (statistical outliers)
Leave-one-out analysis to assess the influence of individual studies
8. Publication Year:
Restricting analysis to more recent studies (e.g., published after 2015)
Comparing results between older and newer studies
9. Funding Source:
Excluding industry-funded studies
Comparing results between industry-funded and non-industry-funded studies.

Country(ies) involved China.

Keywords Knee osteoarthritis; Network meta-analysis; WOMAC; VAS; Non-surgical treatment; Randomized controlled trial.

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