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Research Article

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Allogeneic Umbilical Cord Mesenchymal Stromal Cells for Knee Osteoarthritis: Systematic Review and Meta-Analysis of Controlled Injection Trials

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Abstract

Background

Knee osteoarthritis is a leading cause of chronic pain and reduced mobility worldwide. Intra-articular corticosteroids and hyaluronic acid injections are commonly used, but many patients experience limited durability of symptom improvement. Allogeneic umbilical cord derived mesenchymal stromal cells (UC-MSCs) have emerged as a regenerative medicine strategy intended to modulate inflammation and improve clinical outcomes.

Objective

To evaluate controlled clinical trial evidence for intra-articular allogeneic UC-MSC therapy in symptomatic knee osteoarthritis, with emphasis on durability of pain improvement at 12 months.

Methods

A systematic review was conducted to identify controlled clinical trials evaluating intra-articular allogeneic UC-MSCs for knee osteoarthritis with comparator injection arms. The primary endpoint was WOMAC pain at 12 months. Secondary outcomes included WOMAC total at 12 months. When trials did not provide numeric endpoint values in tables, values were extracted from published figures as estimated mean and dispersion measures. Outcomes were synthesized under a random effects framework with consideration of comparator type (hyaluronic acid vs corticosteroid).

Results

Two controlled trials met criteria for quantitative synthesis at 12 months. Across comparator subgroups, UC-MSC therapy demonstrated lower WOMAC pain scores at 12 months compared with control injections. UC-MSC therapy also demonstrated lower WOMAC total scores at 12 months relative to comparator injection arms. One phase I single-arm study was included in qualitative synthesis for feasibility and safety interpretation but was not eligible for pooled analysis.

Conclusion

Controlled clinical trial evidence suggests intra-articular allogeneic UC-MSC therapy may provide durable improvements in knee osteoarthritis pain at 12 months compared with standard injection-based comparators. Larger randomized trials with standardized reporting are needed to further define efficacy, durability, and safety across broader populations.

Keywords: Knee Osteoarthritis, Umbilical Cord Mesenchymal Stromal Cells, Allogeneic Stem Cells, Regenerative Medicine, Womac, Intra-Articular Injection, Meta-Analysis

1. Introduction

Knee osteoarthritis is among the most prevalent causes of chronic pain, impaired mobility, and functional decline. Symptom burden often progresses over time, contributing to reduced activity

tolerance and loss of quality of life.

Standard injection-based therapies such as intra-articular corticosteroids and hyaluronic acid are commonly used for symptom management. While these approaches can provide benefit in some patients, durability is frequently limited and patients often seek strategies associated with longer-lasting improvements in pain and function.

Allogeneic umbilical cord derived mesenchymal stromal cells (UC-MSCs) have gained increased attention in regenerative medicine due to proposed immunomodulatory, anti-inflammatory, and tissue homeostasis effects within the osteoarthritic joint environment. Controlled clinical trials comparing UC-MSC therapy with standard injection approaches offer clinically relevant insight into relative durability and symptom improvement.

The objective of this study was to systematically evaluate controlled clinical trial evidence for intra-articular allogeneic UC-MSC therapy in symptomatic knee osteoarthritis, with emphasis on WOMAC pain outcomes at 12 months. Secondary evaluation of WOMAC total outcomes was also performed to support interpretation of overall symptom and functional improvement.

2. Methods

- **Reporting Standards**

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The completed PRISMA 2020 checklist is provided as a supplementary file.

PRISMA 2020 Checklist

Manuscript: Intra articular allogeneic umbilical cord mesenchymal stromal cells for knee osteoarthritis a systematic review and meta-analysis of controlled trials

Section and Topic	Item #	Checklist Item	Reported in Manuscript
TITLE	1	Identify the report as a systematic review	Title page
ABSTRACT	2	See PRISMA 2020 for Abstracts checklist	Abstract section
INTRODUCTION	3	Describe rationale for the review	Introduction
INTRODUCTION	4	Provide explicit statement of objectives	Introduction (final paragraph)
METHODS – Eligibility criteria	5	Specify inclusion and exclusion criteria	Methods – Eligibility Criteria
METHODS – Information sources	6	Specify all databases, registers, and other sources searched	Methods; Declarations Data Availability
METHODS – Search strategy	7	Present full search strategy	Methods (database search described; search terms available upon request)
METHODS – Selection process	8	Specify methods used to decide whether studies met criteria	Methods – Study Selection; PRISMA Flow Counts in Results

METHODS – Data collection process	9	Specify methods of data extraction	Methods – Data Extraction
METHODS – Data items	10a	List outcomes and definitions	Methods – Outcomes
METHODS – Data items	10b	List other variables collected	Methods – Data Extraction
METHODS – Risk of bias assessment	11	Specify risk of bias methods	Methods – Risk of Bias
METHODS – Effect measures	12	Specify effect measures for outcomes	Methods – Statistical Analysis
METHODS – Synthesis methods	13a	Describe process to determine study eligibility for synthesis	Methods – Eligibility Criteria
METHODS – Synthesis methods	13b	Methods for preparing data	Methods – Data Extraction
METHODS – Synthesis methods	13c	Methods for tabulating or visually displaying results	Tables 1 and 2
METHODS – Synthesis methods	13d	Describe synthesis methods and model used	Methods – Statistical Analysis (random effects framework)
METHODS – Synthesis methods	13e	Methods to explore heterogeneity	Methods – Statistical Analysis (comparator subgroup analysis)
METHODS – Synthesis methods	13f	Sensitivity analyses	Not performed due to limited number of trials
METHODS – Reporting bias assessment	14	Methods used to assess reporting bias	Not formally assessed due to limited study number
METHODS – Certainty assessment	15	Methods to assess certainty of evidence	Discussion – Certainty of Evidence (GRADE)
RESULTS – Study selection	16a	Describe results of search and selection process	Results – Study Selection (PRISMA Flow Counts)
RESULTS – Study selection	16b	Cite excluded studies and reasons	Results – Study Selection
RESULTS – Study characteristics	17	Present characteristics of included studies	Table 1

RESULTS – Risk of bias	18	Present risk of bias assessments	Results – Risk of Bias Summary
RESULTS – Results of individual studies	19	Present summary statistics for each study	Table 2
RESULTS – Results of syntheses	20a	Summarize characteristics and risk of bias among contributing studies	Results – Risk of Bias Summary
RESULTS – Results of syntheses	20b	Present results of statistical syntheses	Results – Primary and Secondary Outcomes
RESULTS – Results of syntheses	20c	Present investigations of heterogeneity	Comparator subgroup interpretation described in Results
RESULTS – Results of syntheses	20d	Sensitivity analyses	Not performed
RESULTS – Reporting biases	21	Present assessment of reporting biases	Not formally assessed
RESULTS – Certainty of evidence	22	Present certainty of evidence assessment	Discussion – Certainty of Evidence (GRADE)
DISCUSSION – Interpretation	23a	Provide general interpretation of results	Discussion (first 3 paragraphs)
DISCUSSION – Limitations	23b	Discuss limitations of evidence	Discussion – Limitations
DISCUSSION – Limitations	23c	Discuss limitations of review process	Discussion – Limitations
DISCUSSION – Implications	23d	Discuss implications for practice and research	Discussion; Conclusion
OTHER INFORMATION – Registration	24a	Provide registration information	Not registered
OTHER INFORMATION – Protocol	24b	Indicate where protocol can be accessed	No published protocol
OTHER INFORMATION – Amendments	24c	Describe protocol amendments	Not applicable

OTHER INFORMATION – Support	25	Describe sources of financial/non-financial support	Funding section
OTHER INFORMATION – Competing interests	26	Declare competing interests	Conflict of Interest Statement
OTHER INFORMATION – Availability of data, code, materials	27	Report availability of materials	Data Availability section

- **Study Design**
  This study was conducted as a systematic review and meta-analysis of controlled clinical trials evaluating intra-articular allogeneic UC-MSC therapy for knee osteoarthritis.

- **Eligibility Criteria**
  Studies were eligible if they met the following criteria: human clinical trials enrolling adult patients with symptomatic knee osteoarthritis; intra-articular administration of allogeneic umbilical cord derived or umbilical cord tissue derived MSCs; inclusion of a comparator injection arm (placebo, sham, or active comparator); and reporting of WOMAC pain outcomes with follow-up available at, or near, 12 months.

  Studies were excluded if they were reviews or meta-analyses, preclinical investigations, extracellular vesicle or secretome-only therapies without live MSC administration, or lacked a controlled comparator arm. Single-arm early-phase studies were retained for qualitative synthesis of feasibility and safety where appropriate.
- **Outcomes**
  Primary outcome: WOMAC pain at 12 months.
  Secondary outcome: WOMAC total at 12 months.
  Additional outcomes included adverse events and supportive imaging findings when reported.

- **Data Extraction**
  Study characteristics, comparator type, sample sizes, intervention protocols, and outcomes were extracted. When numeric outcome values were not provided in table format, values were extracted from published figures based on graphical presentation of mean values and dispersion measures. Extracted figure-based values were treated as approximations and were transparently described.

- **Risk of Bias**
  Risk of bias was assessed using structured domains aligned with randomized trial methodology, including randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.
- **Statistical Analysis**
  Outcomes were interpreted using a random effects synthesis framework due to expected clinical and methodological heterogeneity. Comparator type was evaluated as a clinical subgroup (hyaluronic acid vs corticosteroid). Given the limited number of controlled studies, quantitative findings were interpreted cautiously as an early synthesis of controlled evidence.

- **Protocol and Registration**
  This study is a systematic review and meta-analysis of previously published controlled trials and does not constitute a prospective clinical trial conducted by the authors. Therefore, clinical trial registration is not applicable.

3. Results

Study Selection (PRISMA Flow Counts)
Records identified through database searching: 36
Records screened (title/abstract): 36
Records excluded after title/abstract screening: 30
Full-text articles assessed for eligibility: 6
Full-text articles excluded: 3
Studies included in qualitative synthesis: 3
Studies included in quantitative synthesis (meta-analysis): 2

Reasons for full-text exclusion included review articles, non-controlled designs, or non-eligible interventions.

- **Included Studies**
  Two controlled trials were eligible for pooled quantitative synthesis at 12 months, with active comparator injection arms including hyaluronic acid and intra-articular corticosteroid. One phase I single-arm study evaluating repeated UC-MSC injections was included in qualitative synthesis for feasibility and safety interpretation only.

- **Risk of Bias Summary**
  Overall risk of bias across the included controlled trials was considered low to moderate. Primary limitations were related to modest sample sizes and incomplete numeric reporting of follow-up outcomes in one trial, requiring figure-based data extraction for quantitative synthesis. No evidence of selective

reporting within the primary pain outcome domain was identified.

- **Primary Outcome: WOMAC Pain at 12 Months**
  Across controlled trials, UC-MSC therapy demonstrated lower WOMAC pain scores at 12 months compared with standard comparator injections. In the hyaluronic acid comparator trial, repeated UC-MSC dosing resulted in substantially lower WOMAC pain at 12 months relative to hyaluronic acid control. In the corticosteroid comparator trial, UC-MSC therapy demonstrated sustained improvement through 12 months compared with triamcinolone, supporting a durability advantage relative to intra-articular corticosteroid. Random effects synthesis favored UC-MSC therapy at 12 months for WOMAC pain, with consistent directionality across comparator subgroups. The characteristics of the included studies are summarized in Table 1.

- **Secondary Outcome: WOMAC Total at 12 Months**
  Two controlled trials reported 12-month WOMAC total outcomes comparing UC-MSC therapy with active comparator injections. Across both comparator subgroups, UC-MSC therapy was associated with lower WOMAC total scores at 12 months compared with control injections, supporting broader improvement in symptom severity and function in addition to pain reduction. Extracted outcome data for WOMAC pain and WOMAC total at 12 months are shown in Table 2.

- **Safety and Tolerability**
  No clear signal of severe treatment-related adverse events was identified across controlled trials included in the quantitative synthesis. The phase I qualitative study further supported feasibility and tolerability of repeated UC-MSC administration, though larger controlled trials are required to characterize rare risks and refine optimal dosing strategies.

Study	Design	Intervention	Comparator	Follow-up	Included in meta-analysis
Matas et al., 2019	Randomized controlled phase I/II	UC-MSC intra-articular injection (single vs repeated dosing)	Hyaluronic acid	12 months	Yes
Pico et al., 2025	Randomized, controlled, double-blind pilot trial	Cryopreserved UC-MSC intra-articular injection	Triamcinolone	12 months	Yes
Ao et al., 2023	Phase I, single-arm	Weekly repeated UC-MSC intra-articular injections	None	3 months	Qualitative only

Table 1: Included Studies and Design Characteristics

Study	Comparator	UC-MSC group (n)	Control group (n)	WOMAC pain 12 mo UC-MSC (mean ± SD)	WOMAC pain 12 mo control (mean ± SD)	WOMAC total 12 mo UC-MSC (mean ± SD)	WOMAC total 12 mo control (mean ± SD)	Notes
Matas 2019	Hyaluronic acid	9	8	1.1 ± 1.3	4.3 ± 3.5	4.2 ± 3.9	15.2 ± 11	Numeric table reported
Pico 2025	Triamcinolone	15	15	3.5 ± 2.5	6.5 ± 3.5	16 ± 14	30 ± 13	Estimated from published figure

Table 2: Primary and Secondary Endpoints at 12 Months (Extraction Dataset)

4. Discussion

This systematic review and meta-analysis evaluates controlled clinical trial evidence for intra-articular allogeneic UC-MSC therapy in symptomatic knee osteoarthritis, with emphasis on durability of pain improvement at 12 months. Across controlled trials with active comparator injection arms, UC-MSC therapy demonstrated consistently favorable WOMAC pain outcomes relative to comparator injections including hyaluronic acid and intra-articular corticosteroid.

Durability of symptom improvement is a key clinical priority in knee osteoarthritis. Conventional injection-based therapies may provide temporary symptom relief, whereas UC-MSC therapy in controlled trial settings has demonstrated sustained improvements through 12 months. The consistent direction of benefit across comparator subgroups supports clinical relevance and justifies continued evaluation in larger randomized trials.

The observed clinical improvements may reflect joint microenvironment modulation through immunoregulatory and anti-inflammatory effects that influence pain signaling and functional limitation. Osteoarthritis pain is multifactorial and may improve through reductions in synovial inflammation and inflammatory signaling even when structural imaging endpoints do not uniformly demonstrate change over intermediate follow-up. This dissociation between symptomatic outcomes and imaging findings is consistent with broader osteoarthritis research and regenerative medicine trial experience.

Secondary analyses supported the primary findings. Across controlled trials, UC-MSC therapy was associated with lower WOMAC total scores at 12 months compared with comparator injection arms, suggesting broader improvement in overall symptoms and function in addition to pain reduction.

Safety remains essential in allogeneic cell therapy. Across the controlled evidence included here, no clear signal of severe treatment-related adverse events was identified. Early-phase repeated dosing data further support feasibility and tolerability, though larger controlled trials are required to establish rare risk profiles and confirm optimal dosing strategies.

5. Limitations

This analysis is limited by the small number of controlled trials currently available for quantitative synthesis, variability in comparator injection type, and differences in dosing strategies across studies. Additionally, complete numeric endpoint values were not uniformly reported in all included trials, requiring figure-based extraction for at least one 12-month outcome. Despite these limitations, the controlled study designs and consistent directionality of outcomes across comparator subgroups support a meaningful durability signal warranting further controlled investigation.

- Clinical Relevance
  Intra-articular corticosteroids and hyaluronic acid are commonly used for knee osteoarthritis symptom management, but many patients experience limited durability of improvement. Controlled trial evidence synthesized here suggests allogeneic UC-MSC therapy may provide greater long-term symptom improvement at 12 months compared with standard injection approaches, supporting potential clinical value for patients seeking longer-lasting outcomes.

- Certainty of Evidence (GRADE)
  Certainty of evidence for WOMAC pain at 12 months was considered low to moderate due to the limited number of controlled trials, modest sample sizes, and comparator heterogeneity. Despite these limitations, directionality of benefit was consistent across comparator subgroups.

6. Conclusion

Controlled clinical trial evidence suggests intra-articular allogeneic UC-MSC therapy may provide durable improvements in knee osteoarthritis pain at 12 months compared with standard injection-based comparators. While the controlled evidence base remains limited, consistent directionality of benefit supports continued evaluation in larger randomized trials designed to define durability, comparative efficacy, and safety in broader patient populations [1-3].

Author Contributions

Kirk Sanford conceptualized the study, supervised project execution, and contributed to manuscript drafting and final review.
Félix Porras contributed to clinical interpretation, regenerative medicine context, and critical revision of the manuscript.
Fergie Martínez contributed to regenerative protocol interpretation, clinical relevance of outcome measures, and manuscript review and editing.
Hugo Ramos contributed to imaging and diagnostic interpretation and reviewed the manuscript for clinical accuracy.
Janine Zamitiz contributed to patient-centered clinical framing, manuscript review, and editorial refinement.
Carlos Green contributed to technical evaluation of treatment protocols and data organization supporting the analysis.
Edward Ramsay contributed to scientific review, interpretation of clinical lab and biomarker relevance, and manuscript review and editing.
All authors reviewed and approved the final manuscript.

Declarations

Ethics Approval and Consent to Participate
Not applicable.

Consent to Publish

Not applicable.

Data Availability

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

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