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Review Article

Therapeutic Modality of Mesenchymal Stem Cells for Moderate to Severe Knee Osteoarthtritis: A Systematic Review

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ABSTRACT

Background: Osteoarthritis (OA) is a chronic degenerative joint disease that commonly affects weight-bearing joints, such as the knee. A potential treatment is the intra-articular injection of mesenchymal stem cells (MSCs), which may stimulate joint tissue regeneration, cartilage formation, and angiogenesis. This systematic review aimed to evaluate the efficacy and safety of MSC therapy in moderate-to-severe knee OA.
Methods: Literature searches were conducted using PubMed, Science Direct, Taylor and Francis, Google Scholar, Springer Link, Wiley, and the Garuda Portal. From the 644 identified articles, only seven randomized controlled trials published within the last 10 years met the inclusion criteria.
Results: Five of the seven studies demonstrated significant reductions in pain based on Visual Analog Scale (VAS) scores following MSC injections. Four studies reported significant improvements in WOMAC scores, whereas one study showed no notable change. Adverse effects noted after injections included joint swelling, contusions, postprocedural hematomas, mild effusion, and injection site pain.
Conclusions: Intra-articular MSC therapy shows potential for reducing pain and improving joint function in moderate-to-severe knee OA. Improvements in VAS and WOMAC scores suggest clinical benefits that can last up to 12–48 months post-treatment. MSC injections may be considered as a causal therapy in addition to symptomatic treatments, such as analgesics, to enhance patient quality of life.

Keywords: Osteoarthritis; Intraarticular mesenchymal stem cells injection; Pain score; Non-communicable disease; Chronic disease

INTRODUCTION

Osteoarthritis (OA) is a chronic and degenerative joint disease characterized by progressive deterioration of articular cartilage, subchondral bone, and surrounding soft tissues. The pathogenesis of OA is multifactorial, involving the interplay of genetic, mechanical, and environmental factors, with weight-bearing joints, such as the knee, being particularly vulnerable due to their high mechanical stress and functional demands. Knee OA ranks 11th as a cause of disability worldwide and 38th as a pathological cause that can reduce the quality of life for those affected. OA can impact various aspects of life, including physical function, psychological function, social aspects, and economic factors for both patients and their families.[1]

Global data indicate that there are 240 million people worldwide aged over 60 years who experience symptomatic OA. The female population has a higher percentage (18%) than the male population (10%). Meanwhile, data released by the Global Burden of Diseases (GBD), Injuries, and Risk Factors Study state that the average incidence

of knee OA reaches 181.2 per 100,000 population, with a trend that has been continuously increasing since 1990.[2,3]

Based on its underlying etiology, it yields two main categories: primary OA, which arises from inherent joint degeneration, and secondary OA, which results from extrinsic factors or pre-existing joint abnormalities. Primary OA is caused by various factors, including mechanical stress, inflammation, metabolism, immune factors, and genetics. Secondary OA is caused by trauma, congenital joint dysplasia, and iatrogenic injury. Risk factors that can increase the incidence of knee OA include degenerative factors, a history of knee trauma, obesity, anatomical alignment abnormalities in the lower extremities, female gender, a history of high intensity physical activity over a long period, and genetic susceptibility.[4]

A recent study indicated that low-grade inflammatory processes might enhance disease symptoms and accelerate disease progression. Certain catabolic products from the cartilage matrix likely stimulate macrophages and other innate immune cells to secrete inflammatory cytokines, consequently accelerating cartilage damage by affecting chondrocyte function. The regulation of signaling pathways related to the acute-phase response, complement, and coagulation in the joint fluid of patients with OA has been documented, indicating that inflammation may play a role in joint damage. The impact of genetic factors was approximately 70%. Research on candidate genes and genomic analysis has discovered polymorphisms or mutations in genes associated with the production of extracellular matrix or inflammation signaling pathways. The genes identified included ADAMTS-12, cartilage intermediate layer protein (CILP), vitamin D receptor (VDR), cyclooxygenase (COX)2, aspirin (ASPN), Growth and Differentiation Factor (GDF)5, and IL4 receptor. The rs20417 polymorphism within the promoter region of the COX2 gene plays a role in the genetic susceptibility to hip and knee OA.[5]

The main symptom of knee OA is pain in the knee joint, which can reduce mobility and impact the quality of life. The symptoms frequently decline over time but can shift enormously depending on the seriousness of the condition. According to the Kellgren and Lawrence (KL) classification, there are four degrees of severity for knee OA, ranging from grade 0 (normal) to grade 4 (severe).[4]

The management of patients with OA must be comprehensive and holistic to reduce the recurrence of symptoms and improve the quality of life. Non-pharmacological management options include engaging in exercises focused on strengthening muscle strength, aerobic activities, water-based exercise therapy, physiotherapy, and weight management. In the pharmacological management of osteoarthritis (OA), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly employed, either orally or topically, to modulate pain and inflammation by inhibiting the production of pro-inflammatory prostaglandins. Surgical management may also be considered if OA patients do not show improvement with pharmacological or non-pharmacological therapies.[6,7] There are various surgical therapy options, including osteotomy, unicompartmental knee arthroplasty (UKA), and Total Knee Arthroplasty (TKA). Recently, intra-articular interventional therapy has emerged as an alternative treatment to alleviate the symptoms of OA. Current interventional regimens include corticosteroid injections, platelet-rich plasma (PRP), hyaluronic acid, autologous conditioned serum (ACS), and mesenchymal stem cells (MSC).[7,8]

Mesenchymal stem cells are multipotent progenitor cells that can be harvested from a diverse range of tissue sources, including bone marrow, Wharton's jelly, skeletal muscle tissue, periodontal ligaments, synovial tissue, umbilical cord, umbilical cord blood, amniotic fluid, placenta, and adipose tissue derived from subcutaneous, abdominal, or infrapatellar fat pads. MSC-based therapy is known to trigger articular regeneration by stimulating the formation of fibrous and fibrocartilaginous tissues and enhancing the potential for chondrogenesis in joints. Additionally, MSC therapy regimens can stimulate angiogenesis, cell survival, and cellular differentiation. MSC therapy also has the advantage

of being minimally invasive compared to knee arthroplasty. Additional research is necessary to fully elucidate the therapeutic efficacy of mesenchymal stem cell regimens in the management of knee osteoarthritis (OA), with the ultimate goal of improving patient quality of life.[9,10] This systematic review intends to thoroughly assess the current evidence regarding the efficacy and safety of MSC therapy in patients with moderate-to-severe knee osteoarthritis.

METHODS

Protocol

This study is a literature review conducted using a systematic review method. The research protocols followed the Recommended Reporting Elements for Systematic Reviews and Meta-Analyses (PRISMA). The study was conducted between March and May 2024.

Literature Search

The method for searching literature involved utilizing online databases sourced from PubMed, Science Direct, Taylor and Francis, Google Scholar, Springer Link, Wiley, and Garuda Portal along with these specific keywords: severe knee osteoarthritis OR grade III knee osteoarthritis OR grade IV knee osteoarthritis AND intra-articular mesenchymal stem cells injection AND pain score or knee function. The search for articles was conducted between April 1 and May 1, 2024.

Inclusion and Exclusion Criteria

The criteria for including studies in this research comprised full articles published in English, with a release date within the past decade (2014-2024). Additionally, the selected studies must have a randomized controlled trial (RCT) design and focus on evaluating the safety and effectiveness of MSC injection therapy within the joints for individuals diagnosed with osteoarthritis grades 2 to 4. Effectiveness was evaluated based on changes in WOMAC and VAS scores, while safety was assessed based on side effects. The exclusion criteria for this study were review articles, articles that were not open access, incomplete clinical trials, information that was not sufficiently clear, and articles that were not full text.

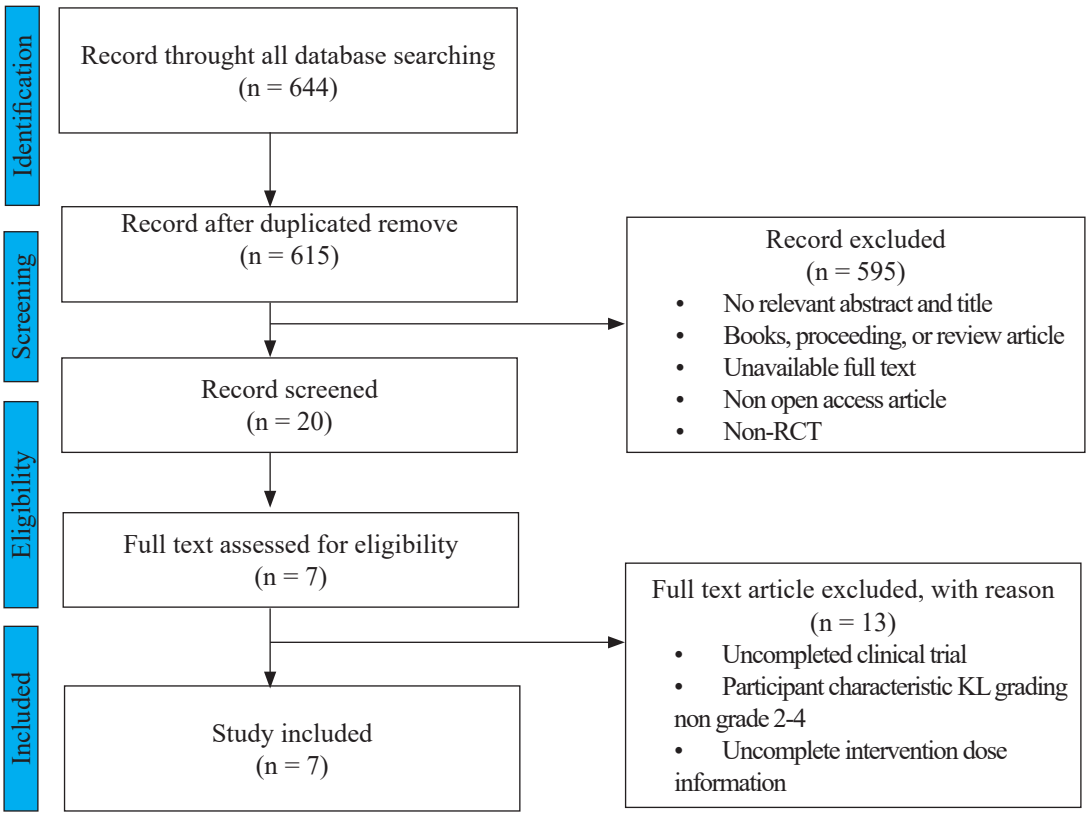

Figure 1. PRISMA flowchart of article search and selection

Data Collection

Data extraction was performed by three researchers (IJ, NJ, and MH). The results of the data extraction are displayed in Microsoft Excel, as shown in Table 1. Study selection and risk of bias assessment were conducted independently by two reviewers (IJ, NJ). Discrepancies were resolved through discussion or consultation with a third reviewer (MH).

Data Exctraction

The final inclusion data were gathered, which encompassed the researcher's name, title of the study, year it was published, methodology used, attributes of the study participants, interventions carried out, and the results of the research evaluated on the basis of whether side effects were present or not, as well as the effectiveness and safety of the intervention given.

Risk of Bias

Articles that fulfill the inclusion requirements will subsequently be evaluated for bias risk using the Revised Tool for Risk of Bias in Randomized Trials, known as RoB 2.0.

RESULT

A search for articles was conducted through PubMed, Science Direct, Taylor and Francis, Google Scholar, Springer Link, Wiley, and the Garuda Portal, resulting in 644 articles from all search engines. The researchers eliminated duplicate articles, leaving 615 remaining articles. Based on the inclusion criteria, 20 articles were found to meet the criteria, and 13 of those fell into the exclusion criteria due to incomplete clinical trials, participant characteristics not meeting KL 2-4 classification, and incomplete information on the intervention dosage provided. Thus, the final results consisted of seven research articles (Figure 1). The assessment of bias risk using RoB 2.0, yielded four articles with low risk, one article with some concern, and two articles with high risk (Figure 2). The results of the data extraction are shown in Table 1.

Based on the RCT carried out by Mautner et al., which examined the effectiveness and safety of intra-articular injections involving corticosteroids, autologous bone marrow aspirate concentrate (BMAC), mesenchymal stromal cells

Figure 2. Risk of bias analysis

derived from umbilical cord tissue (UCT), and stromal vascular fraction (SVF), the results indicated that corticosteroids did not demonstrate any better functional outcomes than the other three orthobiological agents. The evaluation of changes in VAS scores from the beginning of the study to 12 months post-intervention showed no significant differences after the injections, with P values of 0.19 (BMAC), 0.56 (SVF), and 0.76 (UCT). Comparable findings emerged in the KOOS Score evaluation, showing *p* values of 0.49 for BMAC, 0.82 for SVF, and 0.44 for UCT. MRI examinations did not reveal any significant changes among the four groups compared to the baseline data. Safety assessments indicated no serious side effects, such as infections or allergic reactions. However, various mild side effects were noted after the intervention. In the UCT group, there were reports of joint swelling in 28 cases (24.1 %), compared to the control group, which had only eight cases (7.4 %) ($p = 0.01$). Post-procedural contusions also occurred in two groups: 38.6% in the SVF group and 12.2% in the BMAC group, while post-procedural hematoma was reported in 2.9% of the BMAC group and 12.4% of the SVF group.[11]

The study carried out by Shadmanfar et al., which evaluated the effectiveness of MSC injections into joints against a placebo, indicated that these MSC injections can notably alleviate pain within six months following the injection. The VAS score showed a reduction of -20.8 in the group that received the intervention, while the control group experienced a decline of -15.7 ($p = 0.65$). Additionally, the intervention group demonstrated a noteworthy decrease in the WOMAC score, with results showing WOMAC Total I>C (25.7 > 5.5) $p = 0.01$; WOMAC Pain I>C (35 > 12.2) $p = 0.001$, in comparison to the control group. This research indicated that there were no notable adverse effects among the participants after the intervention.[12]

A different research project carried out by Lamo-Espinosa et al. showed that one year after high-dose intra-articular bone marrow stem cell (BMSC) injection, patients with knee osteoarthritis experienced a notable reduction in their VAS and WOMAC scores. The VAS score significantly decreased from 7 to 2 ($p = 0.005$) and from 6 to 2 ($p = 0.009$) with low- and high-dose injections, respectively. The study results also indicated a significant reduction in WOMAC scores with high-dose injection from 28 to 16.5 ($p < 0.01$). No serious side effects were observed after the procedure. In this study, patients received NSAID therapy for 24 hours post-intervention.[13]

Lamo-Espinosa et al. carried out a comparable investigation and demonstrated identical findings, revealing that over a span of four years, injections of intra-articular BMSC can lead to a decrease in WOMAC and VAS scores for individuals suffering from knee osteoarthritis. Assessment of the WOMAC score indicated a significant decrease in the low-dose group from 37 to 17 ($p = 0.01$). The VAS score also experienced a significant reduction at both BMSC doses, with a decrease in the low-dose group from 7 to 2 ($p = 0.01$) and in the high-dose group from 6 to 3 ($p = 0.004$). Within the control group given intra-articular hyaluronic acid treatments, there was no notable reduction noted in the WOMAC or VAS assessments. Additionally, this research indicated that none of the participant groups reported any major adverse effects.[14]

Similar results were obtained in a study conducted by Lamo-Espinosa et al. The research showed a decrease in VAS and WOMAC scores after the administration of a combination injection of PRGF and BM-MSC, although the results were statistically insignificant (VAS Score C < I (5 to 4.5, $p = 0.0389$ vs 5.3 to 3.5, $p = 0.01$), WOMAC score C < I (31.9 to 22.3, $p = 0.002$ vs 33.4 to 23.0, $p = 0.053$). This study also found no side effects occurring in the research subjects.[15]

A study conducted by Vega et al. demonstrated a notable reduction in VAS scores after intra-articular MSC injections. In this study, no major side effects were observed in either the control or intervention groups. The analgesic effect produced after MSC administration could reach 38% to 42%, compared to the analgesic effect observed in the control group, which was only 10% to 14%.[16]

Khalifeh et al. conducted a study and obtained different results, as the intra-articular injection of allogenic placenta-derived MSC was found not to significantly reduce the VAS score (p = 0.401) after six months of observation. There were side effects reported in this study, including pain at the injection site and mild effusion, which gradually subsided 48-72 hours after the injection.[17]

Based on the explanation above, it can be concluded that out of the seven studies conducted, five showed a significant decrease in VAS scores after intra-articular injection, whereas the other two indicated no significant change in VAS scores following the intervention. Additionally, a decrease in WOMAC scores was found after the intervention in four studies, whereas another study showed no significant change in WOMAC scores post-intervention. Side effects noted after MSC injection included swelling in the joints, bruising after the procedure, hematoma following the procedure, slight fluid accumulation, and discomfort. The side effects were considered insignificant, as they tended to improve on their own over time.

DISCUSSION

According to the findings, most of the studies reviewed suggest that patients with moderate to severe knee osteoarthritis experience enhanced VAS and WOMAC scores after receiving intra-articular MSC injections. This suggests that intra-articular MSC injection has the potential to be an alternative therapy for patients with OA, who have primarily focused on pain relief treatments without considering changes in joint damage. Average clinical improvement begins to be observed 1–4 years post-intervention.

The MSC approach applied in this study mainly focuses on mesenchymal stem cells from the bone marrow. Bone marrow stem cells offer benefits compared to various other stem cell types because they have the ability to transform into mesodermal lineages, including bone, cartilage, and fat cells, along with additional lineages that originate from ectodermal and endodermal cell types. Additionally, MSC injections can differentiate into specific cells that contribute to the repair of damaged tissue.[18] Numerous research efforts have shown that bone marrow mesenchymal stem cells (BM-MSC) possess a higher ability for osteogenic and chondrogenic differentiation. BM-MSC can enhance the formation of bone and cartilage and improve the regeneration of more mature and denser bone tissue. Research findings also indicate that BM-MSC express high levels of CD90. The increase in this marker suggests enhanced bone repair and regeneration due to BM-MSC stimulation.[19]

The research conducted by Vega et al. regarding allogeneic marrow stem cell therapy for patients with OA who do not respond to conservative treatments indicates that the pain relief provided by allogeneic MSC therapy is significant, yielding a pain reduction of 38% to 42% compared to 10% to 14% with active control using hyaluronic acid. The impacts were notable at 6 and 12 months for patients treated with MSC. Assessment of cartilage quality through T2 relaxation measurements indicated a notable reduction in areas of poor cartilage, along with enhancements in cartilage quality among patients treated with MSCs.[16]

MSCs contribute to the creation of bone in two ways, specifically via endochondral or intramembranous ossification. In the process of endochondral ossification, MSCs transform into chondrocytes and generate cartilage matrix, which is then activated by osteoblasts to facilitate bone formation. In contrast, in intramembranous ossification, MSCs transform directly into osteoblasts. Multiple signaling pathways play a role in the chondrogenic differentiation of MSCs, such as Notch signaling, TGF-β, and Wnt/β-catenin. At the same time, several cytokines involved in the process of creating bone are RUNX2, Sox9, TGF-β, FGF, and various other cytokines. The transcriptional regulators involved in this process are influenced by RUNX2, β-catenin, and osterix.[19]

A study carried out by Kim et al. (2023) revealed that injecting autologous culture-expanded Adipose-Derived Mesenchymal Stem Cells (ADMSC) directly into the joint can greatly alleviate discomfort

Table 1. Data extraction results

No	Title	Authors	Year	Place	Duration	Aim and intervention	Result
1.	Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized 3 phase trial	Mautner K *et al.*[11]	2023	USA	12 Months	Measure efficacy dan safety of - (Control) corticosteroid injection 1 mL from depomedrol (40 mg/dL) dissolved in 6 mL NS - (Intervention 1) BMAC 7 mL - (Intervention 2) SVF 5 mL - (Intervention 3) UCT 7 mL Efficacy measured by VAS Score and KOOS pain score before and 12 months after intervention	**[Adverse events]** - Joint swelling (CSI 7.4% vs UCT 24.1%, P=0.01) - Post-procedural contusion (SVF 38.6% vs BMAC 12.2% vs UCT/CSI 0%, P<0.0001) - Post-procedural hematoma (BMAC 2.9% vs SVF 12.4%, P=0.02) **[Efficacy]** - [12 Month VAS Score] C = I1 = I2 = I3 (119 to 97 vs 118 to 95; P=0,19 vs 119 to 91, P=0,56 vs 118 to 98; P=0,76) - [12 Month KOOS Pain Score] C = I1 = I2 = I3 (119 to 96 vs 118 to 95; P=0,49 vs 118 to 92; P=0,82 vs 118 to 98; P=0,44)
2.	Intra-articular implantation of autologous bone marrow-derived mesenchymal stromal cells to treat knee osteoarthritis: a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial	Shadmanfar S *et al.*[12]	2018	Iran	6 Months	Measure efficacy and safety of - (Control) 5 mL NS + 2% albumin serum - (Intervention) Implantation of Intra-articular MSC 40x106 in 5 mL NS with 2% albumin serum	**[Adverse Events]** None **[Clinical Effects]** - WOMAC total after 6 months decreased I>C (25.7 > 5.5) P=0.01 - WOMAC pain after 6 months decreased I>C (35 > 12.2) P=0.001 - VAS score after 6 months decreased I>C (-20.8 > -15.7) P=0.65
3.	Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow up of a multicenter randomized controlled clinical trial (phase I/II)	Lamo-Espinosa JM *et al.*[13]	2018	Spain	48 Months	Measure efficacy and safety - (Control) Intra-articular injection Hyaluronic Acid (HA) 4 mL - (Intervention 1) Intra-articular injection BMSC 10 × 10^6 (Low Dose) + HA 4 mL - (Intervention 2) Intra-articular injection BMSC 100 x 10^6 (High Dose) + HA 4 mL	**[Adverse Events]** - None **[Clinical Effects]** - [4 Years WOMAC reduction] I1 > I2 (37 to 17, P=0.01 > 29 to 16.5, NS) - There is no WOMAC reduction in control group (27 to 27 after 4 years follow up) - [4 Years VAS reduction] I1 > I2 (7 to 2, P=0.01 > 6 to 3, P=0.004) - There is no VAS reduction in control group (5 to 7 after 4 years follow up)

No	Title	Authors	Year	Place	Duration	Aim and intervention	Result
4.	Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II)	Lamo-Espinosa JM *et al.*[14]	2016	Spain	12 Months	Measure efficacy and safety -(Control) Intra-articular injection Hyaluronic Acid (HA) 4 mL -(Intervention 1) Intra-articular injection BMSC 10 × 10^6 (Low Dose) + HA 4 mL -(Intervention 2) Intra-articular injection BMSC 100 x 10^6 (High Dose) + HA 4 mL	**[Adverse Events]** - None **[Clinical Effects]** - [12 month WOMAC reduction] C < I1 <I2 (29 to 13.5 < 37 to 21.5 < 28 to 16.5, P<0.01) - [12 month VAS reduction] C < I1 < I2 (5 to 4 < 7 to 2, P=0.005<6 to 2, P=0.009)
5.	Phase II multicenter randomized controlled clinical trial on the efficacy of intra-articular injection of autologous bone marrow mesenchymal stem cells with platelet rich plasma for the treatment of knee osteoarthritis	Lamo-Espinosa JM *et al.*[15]	2020	Spain	12 Months	Measure efficacy of - (Control) PRGF 8ml - (Intervention) PRGF 8ml + BM-MSC 100x10^6	**[Adverse Events]** - None **[Clinical Effects (Not significant between 2 group)]** - [12 month VAS] C < I (5 to 4.5, P=0.0389 vs 5.3 to 3.5, P=0.01) - [12 month WOMAC reduction] C < I (31.9 to 22.3, P=0.002 vs 33.4 to 23.0, P=0.053)
6.	Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial	Vega A *et al.*[16]	2015	Spain	12 Months	Comparing efficacy of - (Control) IA HA 60 mg - (Intervention) IA MSCs 40 x 10^6 cells 8 mL	**Clinical effects : (Significant)** - VAS - WOMAC - Lequesne index - SF-12
7.	Safety and efficacy of allogenic placental mesenchymal stem cells for treating knee osteoarthritis: a pilot study	Khalifeh SS *et al.*[17]	2018	Iran	6 Months	Comparing efficacy of - (Control) Normal saline 10 mL - (Intervention) allogenic placenta-derived MSC 10 ML (0.5-0.6 x 10^8)	**Adverse Effects : (MSC group)** - Local pain - Mild effusion **Clinical effects : (Tidak signifikan)** - VAS (P=0.401) **Clinical effects : (Signfikan)** - ROM (P=0.044) - KOOS questionnaire (P=0.028) - MRA factor (P=0.000)

and enhance functionality in individuals with grade 3 knee osteoarthritis. The group receiving ADMSC injections demonstrated a notable enhancement in VAS scores in comparison to the control group (ADMSC vs. Control, 25.2 vs 15.5; p = .004). WOMAC scores also demonstrated a significant decrease compared to the control group (21.7 vs 14.3; p = .002). A comprehensive analysis carried out in 2023 by Kyriakidis et al. additionally verified that intra-articular MSC injections represent a secure and efficient treatment choice for individuals experiencing grade 1-3 osteoarthritis.[20, 21]

The preparation of this literature review has various advantages and limitations that need to be acknowledged. This research has additional strengths because all the literature analyzed consisted of RCT-type studies, which can provide an explicit comparison between MSC-based interventions and placebo-based interventions or the commonly used medication regimens. Furthermore, this study also limited the scope of the search to publications from the last 10 years, specifically from 2014 to 2024. With these advantages, it is hoped that the novelty of the compiled systematic review will be enhanced.

The limitations of this study are that the numerous variations of MSC interventions used (BMSC, MFAT, and MSC) prevent this research from drawing conclusions about the best MSC intervention regimen that can be administered to patients with knee OA. Additionally, this study did not examine the clinical implications regarding the quality of life of respondents after the intervention. With these limitations, it is hoped that this study can serve as a reference for future experimental research.

CONCLUSION

According to a comprehensive analysis of seven studies that included 673 individuals, it can be inferred that intra-articular injections utilizing mesenchymal stem cells may enhance VAS and WOMAC scores in patients with moderate to severe osteoarthritis of the knee. Clinical improvements can be observed 12–48 months post-intervention. The comprehensive research review showed a fairly minimal risk of bias because of the blinding methods used, which can help diminish the possibility of outcome bias for both the participants and the researchers engaged. Therefore, it can be concluded that the administration of intra-articular MSC injections can be considered a causal treatment alongside analgesics for symptomatic management to enhance the quality of life in patients with knee OA.

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CONFLICT OF INTEREST

There are no conflicts of interest regarding the publication of this work. No financial, personal, or professional relationships influenced the research, analysis, or conclusions presented in this manuscript.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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