The Effectiveness of Stem Cells and Their Secretome and Exosome Derivatives as a Treatment for Osteoarthritis: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Osteoarthritis (O.A.) has a significant global prevalence and is one of the most common musculoskeletal diseases. O.A. is defined as chronic inflammation that involves the non-specific immune system. The incidence and years lived with disabilities due to O.A. is increasing in most nations. World Health Organization (WHO) reported that about 528 million people worldwide in 2019 lived with O.A. Patients with O.A. were given analgesics using nonsteroidal anti-inflammatory medications (NSAIDs) to relieve the pain. Other non-surgical options for O.A. are intra-articular injections of hyaluronic acid (H.A.) or steroids. In recent decades, mesenchymal stem cells (MSCs) have appeared as a potential treatment for many illnesses, including O.A. They are the most representative adult stem cells and a key form of the stem cell family, implying that MSCs could be very useful in treating O.A. Therefore, this study aims to investigate and compare the effectiveness of stem cells and their secretome and exosome derivatives as a treatment for O.A.

Method: The studies used in this study originated from online databases (PubMed, Science Direct, Cochrane Library, and Google Scholar), which evaluated the outcomes of stem cells and their secretome and exosome derivatives treatment for O.A. The New Castle and Ottawa Scale for Cohort and Cross-Sectional Studies was used to assess the quality of observational studies, and the quality of trials was evaluated using Cochrane's risk of bias (RoB). Quantitative analysis was carried out using mean difference analysis to determine the overall patient survival rate using Review Manager v.5.4 software. Heterogeneity was evaluated using I-squared and t-squared tests. The risk of publication bias was evaluated using a qualitative funnel plot approach.

Result and Discussion: A total of 22 studies with 1037 participants consisting of 613 OA patients and 424 normal participants. Most studies came from the Asian region, especially Korea and China, and were RCTs. The main source of use of stem cells comes from bone marrow and adipose tissue, with the most common administration method being intra-articular injection. The stem cells group outperformed the comparative group in terms of improvement of cartilage regeneration capacity, visual analog score (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and International Knee Documentation Committee (IKDC) scores after treatment. The quantitative analysis in this study presented a significant overall mean difference between groups from the VAS score and WOMAC ($p<0.05$), in which the stem cells group showed better improvement than the comparative group.

Conclusion: Stem cell treatment is the most promising for joint tissue regeneration. MSCs are the most promising stem cells because they are straightforward to harvest, multiply effectively, do not induce the formation of tumors, and are highly tolerated by the immune system. In general, MSCs show promising results in treating O.A. patients.

INTRODUCTION

OA is defined as chronic inflammation that involves the non-specific immune system. O.A. is an illness that is described by increasing articular cartilage degradation, thickening of subchondral, osteophyte formation, and non-specific synovial inflammation.[1] O.A. is a foremost community health challenge. O.A. has a substantial global prevalence and is one of the most common musculoskeletal diseases.[2]

The prevalence, incidence, and years lived with disability caused by O.A. is rising in most nations. It is expected to continue with increased life expectancy and aging of the world population.[3] In 2032, it is estimated that 30% of people over 45 will have OA.[4] World Health Organization (WHO) reported that about 528 million people in the world in 2019 lived with O.A. It has increased by 113% since 1990. Seventy-three percent of people living with O.A. are older than 55, and most are female (60%).[5] The most common joints affected by O.A. are the knee, hip, and hand, with a prevalence of 365 million.[6] The occurrence of O.A. knee in Indonesia has touched 39 million (15.5%) males and 32 million (12.7%) females from a 255 million population.[7]

OA-related pain and stiffness negatively impact the quality of life (QoL) and daily activities of the patients.[8] Therefore, the principal goal of O.A. treatment is to ease the pain and enhance the patients' function and QoL. The standard procedure for O.A. is symptomatic treatment.[1] Patients with O.A. were given analgesics using nonsteroidal anti-inflammatory medications (NSAIDs) to relieve the pain. Because of the persistent and progressive pain in O.A. cases, the long-term effects of NSAID intake are often undesired and 2.5-5 times more likely to be associated with gastrointestinal illnesses.[2] Other non-surgical options for O.A. are the use of intra-articular injections of hyaluronic acid (H.A.) or steroids for cases that do not respond to the previous treatments.[9]

Mesenchymal stem cells (MSCs) have appeared as a potential treatment for many illnesses, one of them O.A., in recent decades.[8] MSCs are pluripotent adult stem cells that have stem cell properties. They are extracted and grown from the mesoderm and ectoderm of different tissues and organs. They are the most representative adult stem cells and a key form of the stem cell family, implying that MSCs could help treat O.A. and cartilage abnormalities.[10,11] The previous studies have derived MSCs from numerous sites, such as bone marrow, umbilical cord, placenta, adipose tissue, and others. Based on those explanations, this study aims to investigate and compare the effectiveness of stem cells and their secretome and exosome derivatives as a treatment for O.A.

METHODS

This review is carried out by identifying, assessing, and interpreting all findings related to scientific topics. The author used the PICOS (Population, Intervention, Comparison, Outcome, Studies) strategy to identify all relevant studies. All systematic search procedures follow the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Study selection

The studies used in this study were all articles originating from online databases, including PubMed, Science Direct, Cochrane Library, and Google Scholar, which evaluated the outcomes of stem cells and their secretome and exosome derivatives therapy for O.A. The intended result is therapy effectiveness, including corneal tissue regeneration and patient scoring.

The general population in this study were O.A. patients who had been given stem cell therapy. Studies were excluded if studies with populations undergoing definitive therapy other than stem cells and studies that did not clearly state the outcome of therapy.

Study Search

Search for relevant literature or studies using several keywords from the development of PICOS to obtain maximum search findings. In the study search process, the author's first step was determining keywords using Medical Subject Headings (MeSH). After selecting keywords using MeSH, a research journal search technique was carried out using advanced search, bibliographic search, and Boolean operators (AND, OR, and NOT) on keywords arranged according to the research topic. The terms ((stem cells) AND (osteoarthritis)) were used as search terms.

Data extraction and study quality assessment

Overall, this study used critical appraisal to assess the quality of articles that could be included in a systematic review. The author carried out data extraction independently. The quality of observational studies was assessed using the New Castle and Ottawa Scale for Cohort and Cross-Sectional Studies. Meanwhile, the study quality for trials is assessed using Cochrane's Risk of Bias (RoB). If the overall interpretation obtained is quite good, the article is declared to meet the criteria and included in the inclusion criteria, and vice versa.

Data analysis

Data analysis is done by systematically integrating and describing all data to obtain conclusions. The data consists of research characteristics (name of primary author, year of publication, and research location), population characteristics, measurement methods, measurement parameters, and leading research results. Data is loaded in tabular form (synthesis matrix) to facilitate analysis. Quantitative analysis was carried out using mean difference analysis to determine the overall patient survival rate using Review Manager v.5.4 software. Heterogeneity was assessed using I-squared and t-squared tests. Significant heterogeneity values indicate using a random effect model in the analysis. The risk of publication bias was evaluated using a qualitative funnel plot approach. The acceptable significant p-value is <0.05.

RESULTS

Study Search

In the study search process, 6.358 articles were obtained from online databases (PubMed, ScienceDirect, Cochrane, and Google Scholar). Six thousand three hundred fifty articles were obtained after removing duplicates. In the title and abstract screening process, 87 articles were obtained that could be accessed and then assessed for eligibility. In addition, 65 articles were excluded because they did not have complete or relevant data regarding survival rate outcomes, which resulted in qualitative (systematic review) and quantitative (meta-analysis) analyses using 22 included studies. The study search flow using the PRISMA guideline is described as follows **(Figure 1).**

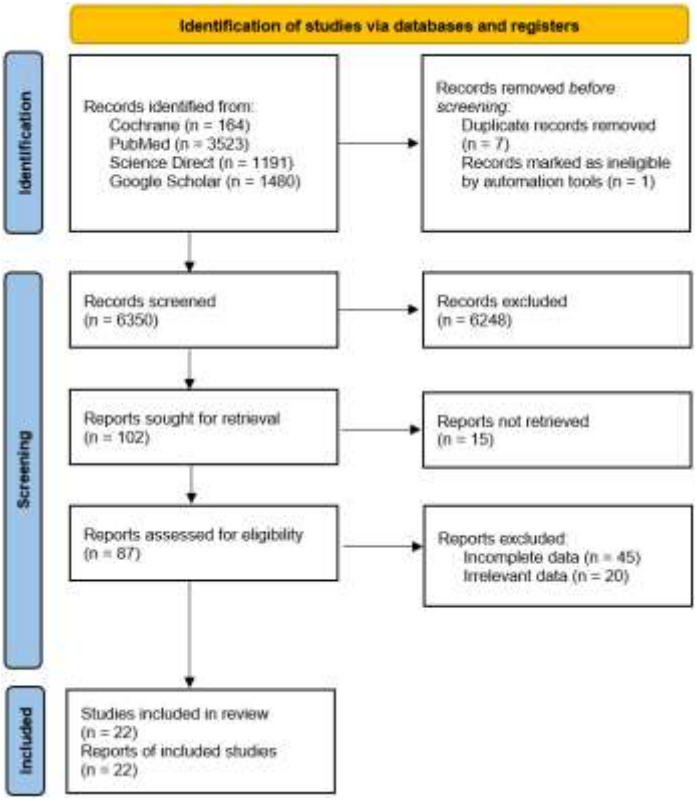

Figure 1. Study search (PRISMA) flowchart

Study characteristics

A total of 22 studies with 1037 participants comprised 613 OA patients, and 424 normal participants were included. Most studies come from the Asian region, especially Korea and China. Most of the studies were RCT studies. The primary source of use of stem cells comes from bone marrow and adipose tissue, with the most common administration method being intra-articular injection. When assessed by disease grade, most studies included patients with Kellgren-Lawrence grade >II. The duration of follow-up studies is mostly around 1 year. Data on study characteristics can be seen in Figure 1.

Table 1. Study characteristics

Authors, year	Study design	Country	Population			Source and site of S.C.s
			Intervention	Comparator	Total	
Chen, 2021[12]	Randomized controlled trial	China	17	8	25	Adipose tissue
Dilogo, 2020[13]	Randomized controlled trial	Indonesia	29	0	29	Umbilical cord
Freitag, 2019[14]	Randomized controlled trial	China	10	10	20	Adipose tissue (abdomen)
Garza, 2020[15]	Randomized controlled trial	USA	13	13	26	Adipose tissue (abdomen)
Hashimoto, 2019[16]	Randomized controlled trial	Japan	7	4	11	Bone marrow
Ho, 2022[17]	Randomized controlled trial	China	10	10	20	Bone marrow
Kim, 2019[18]	Randomized controlled trial	Republic of Korea	40	40	80	Adipose tissue

Kim, 2020[19]	Randomized controlled trial	Republic of Korea	30	30	60	Adipose (gluteal)
Koh, 2016[20]	Randomized controlled trial	Republic of Korea	18	16	34	Adipose tissue (buttock)
Lamo-Espinosa, 2020[21]	Randomized controlled trial	Spain	30	30	60	Bone marrow
Lee, 2019[22]	Randomized controlled trial	Republic of Korea	12	12	24	Adipose tissue (abdomen)
Lee, 2021[23]	Randomized controlled trial	Republic of Korea	32	42	74	Umbilical cord
Lu, 2019[24]	Randomized controlled trial	China	23	24	47	Adipose tissue (abdomen)
Matas, 2018[25]	Randomized controlled trial	Chile	18	8	26	Umbilical cord
Partan, 2023[2]	Randomized controlled trial	Indonesia	15	15	30	Umbilical cord
Sadri, 2023[26]	Randomized controlled trial	Iran	18	18	36	Adipose tissue
Saw, 2021[27]	Randomized controlled trial	Malaysia	36	33	69	Peripheral blood
Soltani, 2018[28]	Randomized controlled trial	Iran	10	10	20	Placenta
Song, 2020[29]	Randomized controlled trial	Republic of Korea	128	0	128	Umbilical cord
Vega, 2015[30]	Randomized controlled trial	Spain	15	15	30	Bone marrow
Venosa, 2022[31]	Randomized controlled trial	Italy	19	19	38	Bone marrow
Wong, 2013[32]	Randomized controlled trial	Singapore	28	28	56	Bone marrow

Study outcomes

Almost all studies report significant improvements in some or all therapy outcome parameters after administering stem cells and their derivatives. Some studies report an improvement in cartilage regeneration capacity. Additionally, the stem cells group outperformed the comparative group in terms of visual analog score (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and International Knee Documentation Committee (IKDC) scores after treatment. The study outcomes are described in Table 2.

Table 2. Study outcomes

Authors, year	S.C.s doses & methods	O.A. grade	Duration of treatment	Main outcomes	Quality of Study and Risk of Bias
Chen, 2021[12]	Intra articular injection (16, 32, 64) × 10^6 cells	Kellgren-Lawrence grade II-III	1 year	ELIXCYTE® group (16M, 32M, 64M) presented a safety profile comparable to that of H.A.	Low risk of bias
Dilogo, 2020[13]	Intra articular injection of 10 × 10^6 units in 2-ml secretome implantation	Kellgren-Lawrence grade I-IV	1 year	Human umbilical cord-derived MSCs may represent a novel regenerative therapy for knee O.A. After six months of injection; this intervention had its most significant impact.	Low risk of bias
Freitag, 2019[14]	Intra articular injection 95.1 million (11.1) cells and 103.9 million (7.7) cells	Kellgren-Lawrence grade II - III	1 year	Autologous ADMSC therapy was associated with clinically significant improvement in pain and function in knee O.A. with symptoms.	Low risk of bias
Garza, 2020[15]	Intra articular injection (low dose; 1.5 x 3 107 SVF cells) and (high dose; 3 x 3 107 SVF cells)	Kellgren-Lawrence grade II - III	1 year	Intra-articular SVF injections can significantly decrease the pain and symptoms of knee O.A. at six months and 1 year.	Low risk of bias
Hashimoto, 2019[16]	Intraarticular injection under arthroscopic surgery	International Cartilage Repair Society (ICRS) grade III	48 weeks	Forty-eight weeks after surgery, the intervention group showed a more excellent KOOS QOL score in comparison with the comparative group, and the mean MOCART score was meaningfully higher in the intervention group than the comparative group.	Low risk of bias
Ho, 2022[17]	Intra-articular injection of 6 mL dose	Kellgren-Lawrence grade II-III	1 year	BM-MSCs meaningfully lower O.A. pain and improve QoL and functional assessment score	Low risk of bias

				compared with comparator (H.A.) at one-year follow-up.	
Kim, 2019[18]	Intraarticular injection under arthroscopic surgery	Kellgren-Lawrence grade III-IV	2-3 year	MSCs implanted alongside allogenic cartilage outperform MSCs implanted alone in cartilage regeneration, as evidenced by improved clinical outcomes.	Low risk of bias
Kim, 2020[19]	Intra-articular injection of 7.1 x 10^6 stromal vascular fraction cells	Kellgren-Lawrence grade I-IV	1 year	While the H.A. group saw more early clinical gains during the first three months of therapy, the MSCs group outperformed the H.A. group in terms of VAS, IKDC, and Lysholm scores one year after treatment.	Low risk of bias
Koh, 2016[20]	Intra articular injection (4.97 x 10^6 cells)	Kellgren-Lawrence grade III - IV	2 years	Intra-articular injection of ADSCs improved the radiologic appearance of lesions and clinical outcomes compared to MFX.	Low risk of bias
Lamo-Espinosa, 2020[21]	Intra-articular injection of 100 × 10^6 units	Kellgren-Lawrence grade ≥ II	1 year	Treatment with BM-MSCs was proven to be a promising treatment approach for knee O.A., with clinical enhancement when the last follow-up compared to control.	Low risk of bias
Lee, 2019[22]	Intra-articular injection (1 × 10^8 cells)	Kellgren-Lawrence grade II-IV	6 months	Intra-articular injection of MSCs showed a significant improvement in functional outcomes.	Low risk of bias
Lee, 2021[23]	Intraarticular injection 2 ml	International Cartilage Repair Society (ICRS) grade IIIB	1 year	For cartilage regeneration in knee O.A., the intervention group procedure outperformed the comparison.	Low risk of bias
Lu, 2019[24]	Intra-articular injection (5 × 10^7 cells)	Kellgren-Lawrence grade I - III	1 year	MSCs may enhance knee function, quality of life (including pain	Low risk of bias

				management), and cartilage regeneration.	
Matas, 2018[25]	Intra articular injection of 10×10^6 units (single dose); Intra articular injection of $10 \times 10^6 \times$ units (repeated dose)	Kellgren-Lawrence grade I-III	1 year	At a one-year follow-up, repeated UC-MSC therapy is safer and better for the comparative group.	Low risk of bias
Partan, 2023[2]	Intra articular injection of 2 mL dose secretome	Kellgren-Lawrence grade II-III	12 weeks	Umbilical cord MSCs secretome intra-articular injections presented better clinical improvement, biomarker changes, and no adverse effects in comparison to H.A. in five weeks.	Low risk of bias
Sadri, 2023[26]	Intra articular injection (100 x 10^6 cells)	Kellgren-Lawrence grade II - III	1 year	Allogeneic AD-MSC administration improves clinical signs and symptoms and is safe.	Low risk of bias
Saw, 2021[27]	Intraarticular injection of 8 mL dose	International Cartilage Repair Society (ICRS) grade III - IV	2 year	The intervention group is safe and has significantly improved clinical and radiologic scores compared to the control group.	Low risk of bias
Soltani, 2018[28]	Intraarticular injection of 0.5-0.6 $x10^8$ unit in 10 mL	Kellgren-Lawrence grade II-IV	24 weeks	A single intraarticular allogenic placental MSC injection in knee osteoarthritis is safe and results in clinical benefits in twenty-four weeks.	Low risk of bias
Song, 2020[29]	Intra articular injection of 0.5 x 10^7 cells/mL contains 1.5 mL of umbilical cord blood-derived MSCs (7.5 x	Kellgren-Lawrence grade I-III	2 year	Based on at least a 2-year follow-up, knee O.A. can be effectively treated by implanting human umbilical cord blood-derived MSCs.	Low risk of bias

	10^6) and 4% HA				
Vega, 2015[30]	Intra-articular injection of 40 × 10^6 units	Kellgren-Lawrence grade II-IV	1 year	Allogeneic MSC therapy could be a viable option for treating persistent knee O.A. The method is easy, does not involve surgery, relieves discomfort, and greatly improves cartilage quality.	Low risk of bias
Venosa, 2022[31]	Intraarticular injection 2 ml	Outerbridge grade IV	1 year	Contemporary regenerative medicine approaches, such as platelet-rich plasma and autologous stem cells, appear to improve cartilage regeneration capacity when combined with more conventional arthroscopic bone marrow stimulation methods.	Low risk of bias
Wong, 2013[32]	Intraarticular injection 2 ml	International Cartilage Repair Society (ICRS) grade II-IV	2 year	Intra-articular injections of cultured MSCs improve short-term clinical and MOCART outcomes in patients.	Low risk of bias

Quantitative analysis

VAS score

A total of 8 studies were involved in the analysis of VAS score differences between groups, where the overall mean difference was -1.72 (random effect; 95% CI -2.35 – -1.09, p<0.0001; heterogeneity; τ^2 =0.0002; I^2 = 72%) (Figure 2). The funnel plot shows symmetry, reflecting low publication risk (Figure 3)

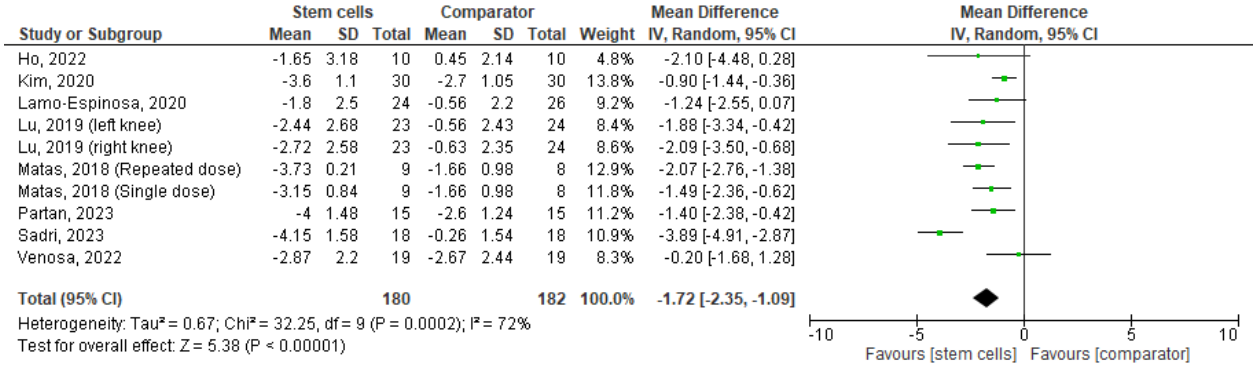

Figure 2. Forest plot of VAS score

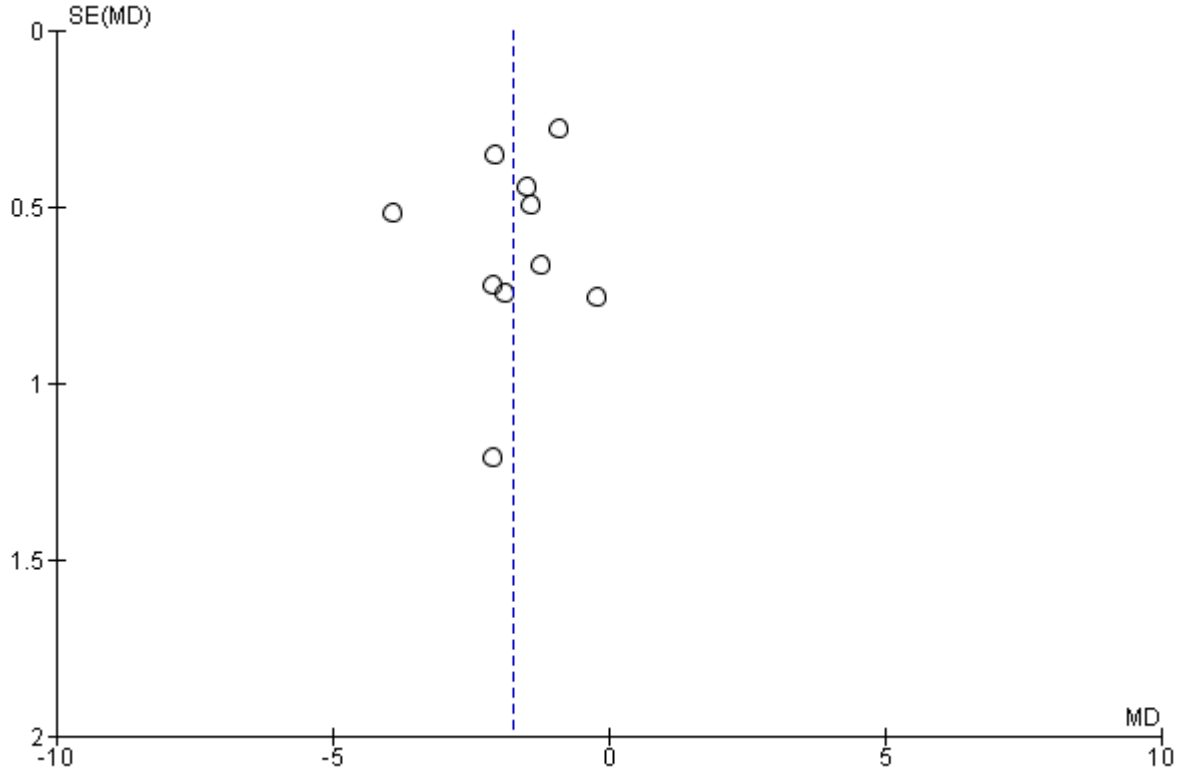

Figure 3. Funnel plot of VAS score

WOMAC

A total of 9 studies were involved in the analysis of WOMAC score differences between groups, where the overall mean difference was -17.66 (random effect; 95% CI -23.68 – -11.64, p<0.0001; heterogeneity; τ^2 =0.0001; I^2 = 81%) (Figure 4). The funnel plot shows symmetry, reflecting low publication risk (Figure 5)

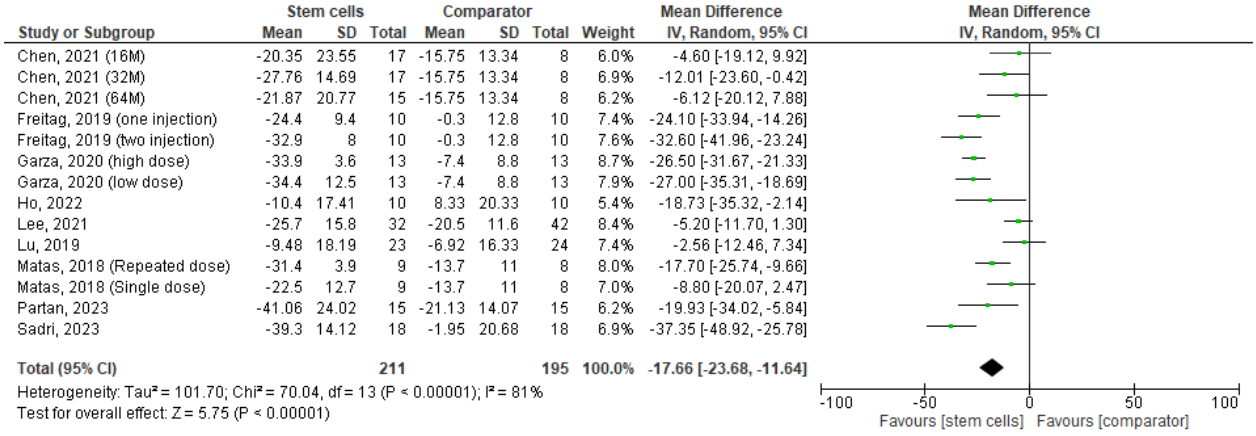

Figure 4. Forest plot of WOMAC score

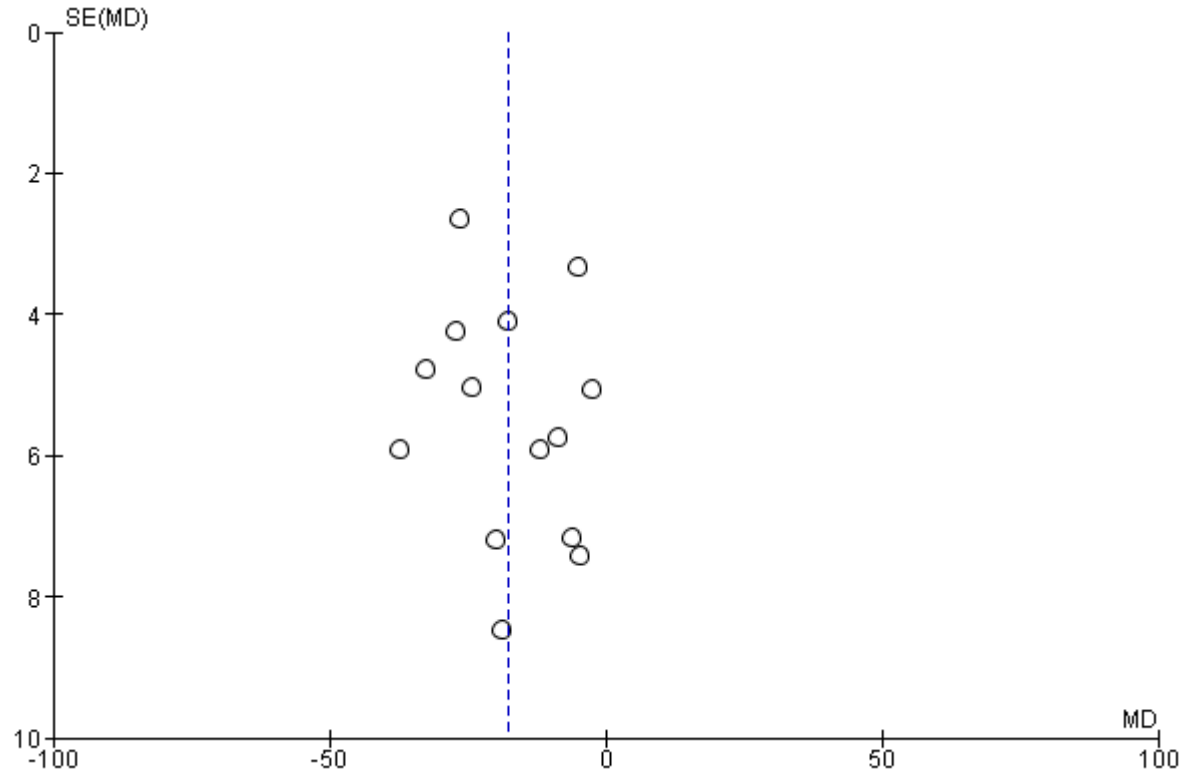

Figure 5. Funnel plot of WOMAC score

IKDC

A total of 4 studies were involved in the analysis of IKDC score differences between groups, where the overall mean difference was 5.64 (random effect; 95% CI -4.81 – -16.10, p=0.29; heterogeneity; τ^2 =0.0001; I^2 = 99%) (Figure 6). The funnel plot shows symmetry, reflecting low publication risk (Figure 7)

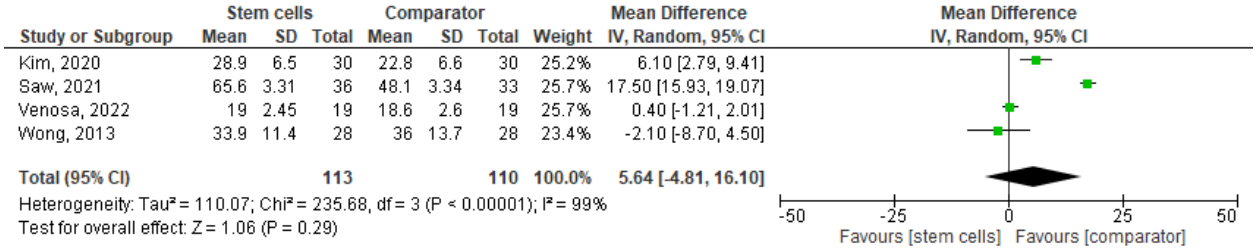

Figure 6. Funnel plot of IKDC score

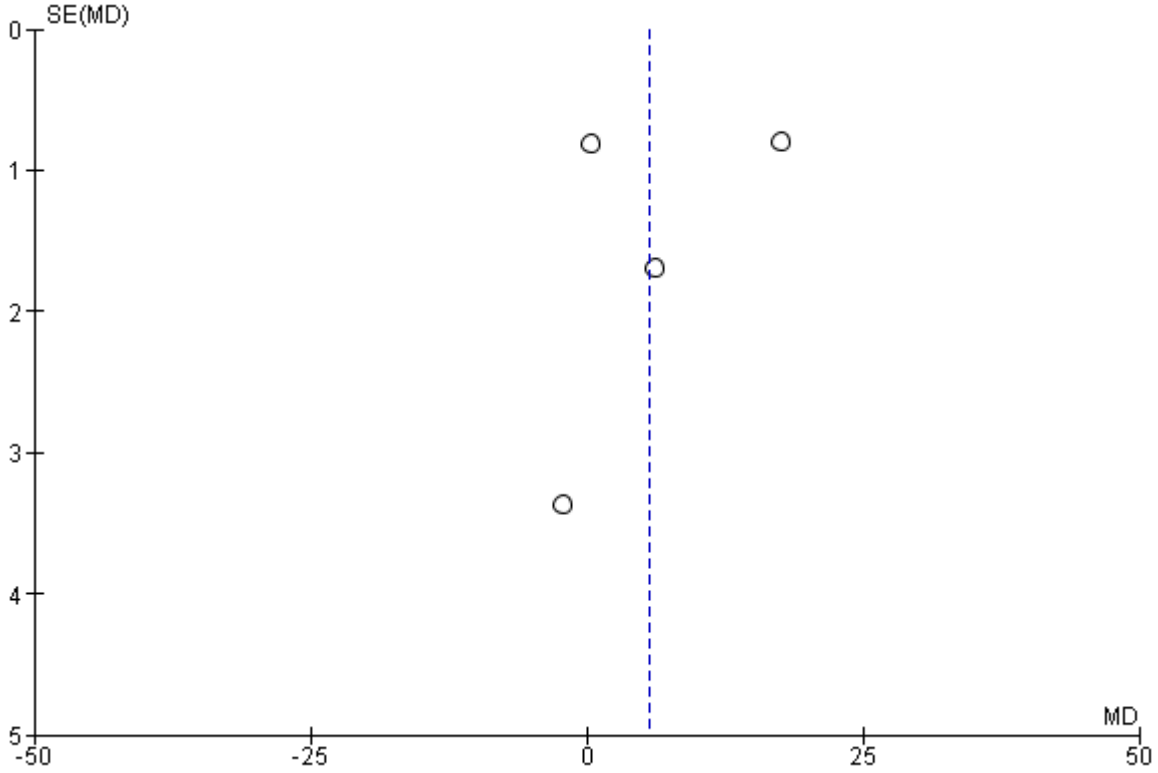

Figure 7. Funnel plot of IKDC score

DISCUSSION

Our study found that MSCs provide good and significant outcomes in O.A. patients. These results align with the meta-analysis by Issa et al. (2022), which included four trials with 138 total patients of O.A. The study discovered that MSCs scored better on WOMAC ratings than controls at 6- and 12-month follow-ups. At the 12-month follow-up, pain, functional, and quality of life ratings similarly preferred MSCs.[33] A meta-analysis done by Long et al. (2022) that comprised 28 RCTs with 1,494 participants revealed a similar result. The study found that with an onset time of no more than three months and a duration of no less than twelve months to sustain the therapeutic effect, MSCs may be a safe medication with good curative efficacy in the treatment of OA.[34]

Since Friedenstein's 1966 description of MSCs, research endeavors to maximize their therapeutic potential have centered around them. Because MSCs are immune-evading, they produce immunomodulatory substances that help them evade rejection mechanisms long enough to take effect in therapy.[35] Adipocytes, osteoblasts, myocytes, and chondrocytes are the only mesodermal-specific cell types that MSCs can typically generate, while some of them can develop into other cell types. Producing bioactive compounds with ant-scarring, angiogenic, immunomodulatory, chemoattractant, and anti-apoptotic properties is one of MSCs' trophic effects.[36,37]

Adult stem cells live in small, specialized microenvironments known as niches. These cells' quantity, activation, proliferation, self-renewal, and lineage differentiation are regulated by a series of factors in their physical anchoring location. The stem cells' homeostatic regulation is up or down-regulated by the niche's microenvironment, including all its components and signaling modulators. Genuine MSCs in adults have been found to originate in a perivascular area close to pericytes and the tunica adventitia. Perivascular stem cells

(PSCs) are the aggregate name for these cells.[38,39] MSCs are formed from pericytes and perivascular cells to originate from any vascularized tissue.[40]

Distinct MSC sources exhibit unique attributes and come with pros and cons. The umbilical cord (UC-MSCs) contains the greatest MSC concentration of any tissue, followed by fat and amniotic fluid.[41] Regarding MSC proliferative capacity, umbilical cord, and amniotic-derived MSCs are superior to fat and bone marrow-derived MSCs. Compared to MSCs derived from bone marrow, placental MSCs have the lowest immunomodulatory capacity. In contrast, MSCs derived from the umbilical cord, amnion, and adipose tissue have the highest immune regulation potential. Umbilical cord MSCs release more cell growth factors than bone marrow MSCs compared to cytokine secretion patterns.[42]

The capability of MSCs to develop into chondrocytes, their capability to stop chondrocyte death, and their ability to stop the degeneration process overall (via a paracrine impact) are some of the benefits of employing them to treat OA.[39] MSCs have much promise for encouraging chondrocyte regeneration and cartilage differentiation.[43] Additionally, they release cytokines and chemokines, block the respiratory burst in neutrophils, reduce T cell proliferation, and influence immune system activity through an immunosuppressive role. The environment can alter how MSCs' pro- and anti-inflammatory characteristics are balanced.[44]

There are several limitations to this study. First, even if the population is tiny, further study is necessary because this intervention is still in its early stages. Second, this research includes global studies overall. Therefore, it cannot single out the effects on specific populations based on geographical differences or characteristics.

CONCLUSION

The scarcity of vascularization in cartilage tissue limits the efficacy of current conventional therapies for O.A. Hence, stem cell treatment appears to be the most promising for joint tissue regeneration, specifically in the mid to late stages of the condition. Of all the stem cell types, MSCs are the most promising since they are easy to harvest, grow efficiently, do not cause tumors to develop, and are well-tolerated by the immune system. MSCs generally show promise in the treatment of individuals with osteoarthritis. However, its application still requires further research involving various populations in a multicenter manner. Besides that, ethical issues regarding this MSC intervention still need to be considered.

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