Review Article Clinical efficacy of mesenchymal stem cells and platelet-rich plasma in the therapy of osteoarthritis: a meta-analysis

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Abstract: Background: Intra-articular administration of mesenchymal stem cells (MSCs) presents a novel methodology for managing osteoarthritis, but there is still no definite evidence of its efficacy. Aim: To assess the comparative effectiveness of MSCs and platelet-rich plasma (PRP) for managing osteoarthritis by reviewing the literature and using meta-analysis. Methods: Randomized controlled trials and cohort studies comparing MSCs and PRP for managing osteoarthritis were included. We searched 'osteoarthritis', 'mesenchymal stem cell', 'platelet-rich plasma', and other words in Pubmed, Embase, and Cochrane Library database. The search period encompassed the entire duration of the databases, starting from its inception until April 2024. Two researchers conducted the literature search, extracting data, and evaluating quality as distinct processes. Meta-analysis was carried out using the software RevMan5.3, and the calculation of weighted mean difference (WMD) and 95% confidence interval (CI) were performed using either a fixed-effect model or a random-effects model. Results: Eleven studies were included, comprising 8 randomized controlled trials and 3 cohort studies. A total of 693 individuals participated in the study, of which 394 received intra-articular injections of MSCs (group A) and 299 received intra-articular injections of PRP (group B). The two groups were comparable in the five dimensions of knee injury and osteoarthritis outcome score (KOOS) [pain (WMD: 0.38, 95% CI: -3.62 to 4.38, P > 0.05), symptoms (WMD: -1.48, 95% CI: -5.90 to 2.94, P > 0.05), activities of daily living (ADL, WMD: -2.36, 95% CI: -6.87 to 2.14, P > 0.05), function in sport and recreation (Sport/Rec, WMD: -3.84, 95% Cl: -10.60 to 2.92, P > 0.05), knee-related quality of life (QOL, WMD: 0.09, 95% Cl: -5.48 to 5.67, P > 0.05)] and Western Ontario and McMaster Universities osteoarthritis index (WOMAC, WMD: 0.47, 95% CI: -3.76 to 4.70, P > 0.05). Compared with group A, the International Knee Documentation Committee Subjective Knee Form (IKDC, WMD: 4.19, 95% CI: 2.57 to 5.82, P < 0.001) score of group B was higher. Conclusion: The short-term effectiveness of intra-articular administration of PRP for managing osteoarthritis is slightly better than that of MSCs. However, because of the limited quantity of incorporated research studies and the potential for bias, requisite in the future are studies of substantial size and superior quality.

Keywords: Mesenchymal cells, platelet rich plasma, osteoarthritis, curative effect, meta-analysis

Introduction

Osteoarthritis is a prevalent degenerative joint disease affecting over half a billion people around the world [1]. At present, the treatment of early osteoarthritis is still limited to antiinflammatory medication, sodium hyaluronate injection, and other conservative treatments. However, these strategies cannot completely prevent the damage of joint tissue or the progress of osteoarthritis, making surgical intervention inevitable. Compared with the need for joint replacement surgery in the late stage, it is particularly important to explore an intervention method that can effectively delay the progression of osteoarthritis and improve the condition of osteoarthritis in the early stage. Cytokines play a significant function in osteoarthritis pathogenesis by regulating various physiological metabolism processes and maintaining normal tissue structure and function [2]. There is increasing research interest in introducing cytokines or cytokine inhibitors into the articular cavity to achieve treatment purposes. Platelet-rich plasma (PRP) is a plasma containing a high concentration of platelets prepared

Proced	ure
#1	("osteoarthritis"[Mesh]) OR (((osteoarthritides[Title/Abstract]) OR (osteoarthrosis[Title/Abstract])) OR (osteoarthroses[Title/Abstract]))
#2	((((((platelet-rich plasma[MeSH Terms]) OR (PRP[Title/Abstract])) OR (plasma rich in growth factors[Title/Abstract])) OR (platelet derived growth factor[Title/Abstract])) OR (platelet derived[Title/Abstract])) OR (platelet gel[Title/Abstract])) OR (platelet rich plasma[Title/Abstract])
#3	((((mesenchymal stromal cell*[Title/Abstract]) OR (mesenchymal stem cell*[Title/Abstract])) OR (mesenchymal progenitor cell*[Title/Abstract])) OR (bone marrow stromal cell*[Title/Abstract])) OR (stem cell*[Title/Abstract])
#4	#1 AND #2 AND #3

 Table 1. Retrieval strategy

by separating autologous whole blood, and it offers numerous growth factors, chemokines, and cytokines essential for cartilage repair. As such, PRP has found widespread use in clinical practice [3]. Mesenchymal stem cells (MSCs) possess self-renewal capabilities along with multi-directional differentiation potential that enables them to regulate immunity, combat inflammation, promote angiogenesis, and facilitate regeneration. MSCs serve as excellent carriers for cytokines and represent a promising new approach for treating osteoarthritis [4]. However, their effectiveness remains under investigation at the present stage, necessitating further study. Hence, we performed a metaanalysis to compare the clinical efficiency of mesenchymal stem cells versus platelet-rich plasma for treating osteoarthritis, aiming to offer guidance in selecting appropriate clinical treatment options, including potential combination therapies.

Methods

PROSPERO statement

This study has been registered with PROSPERO (CRD42024569286).

Inclusion and exclusion criteria

Inclusion criteria: (1) Study design (S): randomized controlled trials, cohort studies; (2) Population (P): patients with osteoarthritis, adhering to clear diagnostic criteria specified in the studies; (3) Comparison (C): patients who received intra-articular injection of MSCs were included in group A; (4) Intervention (I): patients who received intra-articular injection of PRP were included in group B; (5) Outcome (O): outcomes measured include the knee injury and osteoarthritis outcome score (KOOS), Western Ontario and McMaster Universities osteoarthritis index (WOMAC), International Knee Documentation Committee Subjective Knee Form (IKDC). Exclusion criteria: (1) Non-clinical or uncontrolled study; (2) Studies where intervention measures also included other methods other than MSCs and PRP intra-articular injection; (3) Studies where the full text is unavailable or data cannot be extracted; (4) Literature with incomplete research data; (5) Duplicate publications; (6) Literature derived from nonscientific sources such as personal anecdotes, professional viewpoints, or animal studies.

Information sources

Information was sourced by conducting computer-based searches on Pubmed, Embase, and Cochrane Library databases. Relevant research literature on intra-articular administration of MSCs and PRP for treating osteoarthritis was screened. Additional references were traced to supplement the search results. The search timeframe extended from the inception of each database until April 2024.

Search strategy

The search strategy employed English terms such as 'osteoarthritis', 'mesenchymal stem cell', and 'platelet-rich plasma'. The search approach combined subject-specific terms with unrestricted keywords, and the retrieval approach was customized and derived from the database used. For instance, in the case of Pubmed, a detailed outline of the specific search methodology can be found in **Table 1**.

Selection process

Authors Aixirefu and Chen conducted an independent review of the literature. Initially, they scanned the topics and abstracts to exclude any documents that did not meet the requirements. They then carefully read the full text of selected abstracts based on inclusion and exclusion standards to determine their eligibility for inclusion in the study. After completing this process, a cross-check was performed. In case of any disagreements, author Wang was sought for resolution.

Data collection process

Authors Aixirefu and Chen independently collected information based on a standardized data extraction form, which included: (1) General details: paper title, primary author, year of publication, geographical location, and study methodology; (2) Research specifics: sample size, intervention method, grouping, outcome indexes, and measurement data; (3) Research characteristics: design plan, criteria for inclusion and exclusion, and strategies to mitigate bias. After completing this process, a cross-check was performed. In case of any disagreements, author Wang was sought for resolution.

Data items

The primary outcome measures consist of KOOS, IKDC, and WOMAC scores. KOOS was analyzed from five latitudes: pain, symptoms, activities of daily living (ADL), function in sport and recreation (Sport/Rec), and knee-related quality of life (QOL). The study data within 12 months after treatment were extracted.

Study risk of bias assessment

Aixirefu and Chen individually employed the Cochrane bias risk assessment tool and the Newcastle-Ottawa Scale (NOS) to evaluate the quality of included literature. The Cochrane tool was employed to evaluate potential biases across six domains: selection bias, implementation bias, measurement bias, follow-up bias, report bias, and other biases, which were evaluated as 'low risk', 'uncertainty', and 'high risk'. The results of this evaluation were presented in RevMan5.3 software's bias risk map. NOS was used to assess the quality across three aspects: research population selection, comparability, and exposure/outcome. In total, 8 items were evaluated based on a semi-quantitative star system principle. Each item could receive a maximum score of 2 stars except for the comparability module where only up to 1 star was possible. Literature with a total score \geq 6 was classified as high-quality. After completing this process, a cross-check was performed. In case of any disagreements, Wang was sought for resolution.

Effect measures

The weighted mean difference (WMD) was applied as the primary statistical measure for quantitative data analysis, with the 95% confidence interval (CI) calculated for each effect size.

Statistical analysis

The statistical analysis was conducted using RevMan5.3 software. The choice between a fixed effect model and a random effect model was dictated by the degree of heterogeneity observed in the data. Heterogeneity was assessed using I². Acceptable heterogeneity, indicated by P > 0.1 or I^2 < 50%, warranted the use of a fixed effect model. Conversely, if P < 0.1 or $I^2 > 50\%$ showed considerable heterogeneity. Conversely, significant heterogeneity, demonstrated by I² values exceeding 50% or P-values less than 0.1, necessitated the application of a random effect model after excluding non-clinical sources of heterogeneity. Forest plots were used to visually represent the combined effect size from the statistical analysis. All examinations were double-sterned, and P <0.05 was considered statistically significant.

Publication bias assessment

In the presence of variability, an initial examination was conducted to identify potential sources of variation from both methodological and clinical perspectives. Subsequently, subgroup analysis was carried out on factors that could contribute to heterogeneity (such as disease type, stem cell origin, and treatment dosage), or sensitivity analysis may be performed. To detect any possible publication bias, a funnel plot was utilized. Asymmetry in the funnel plot indicates potential bias.



and adipose tissue. Follow-up duration was mostly 12 months, between 6-24 months. At least one outcome indicator was reported in each study, with the three most common indicators highlighted. The key features of the studies incorporated are succinctly outlined in **Table 2**.

Risk of bias in studies

Eight of the included studies [5, 6, 8-11, 13, 15] were randomized controlled trials (RCTs). Due to the use of autologous MSCs, double-blindness between researchers and patients was not feasible, leading to a high risk of blind bias. Additionally, three studies [6, 9, 15] did not explicitly de-

Results

Study selection

Initially, a total of 483 articles were acquired. Automated tools excluded 254 non-randomized controlled trials and non-observational studies, while 68 duplicate articles were excluded by NoteExpree software. By browsing the titles and abstracts. 126 articles with inconsistent research contents and types were excluded. The full text of 35 articles was further obtained. However, exclusions were made for six articles due to inaccessible full texts, eight articles for lacking a control group, three for not including relevant indicators, and seven for data that could not be extracted, resulting in 24 articles being excluded. Ultimately, only 11 studies [5-15] were eligible for analysis. The procedure of screening is depicted in Figure 1.

Study characteristics

All selected papers were published between 2018 and 2024, predominately from the United States. The efficacy of MSCs and PRP in treating osteoarthritis was assessed by comparing the studies included, and the type of disease was knee osteoarthritis. Sample size was small, ranging from 18 cases to 145 cases. The studies utilized MSCs sourced from bone marrow

tail the randomization method, and the selection bias was rated as uncertain. The bias risk assessment findings are depicted in **Figures 2**, **3**. Three studies [7, 12, 14] were cohort studies, of which two studies [7, 12] were prospective cohort studies and one study [14] was a retrospective cohort study. The NOS scores were all \geq 6 points, as shown in **Table 3**.

Results of syntheses

Seven studies [5, 6, 9, 11, 13-15] reported KOOS-pain score, with a total of 485 individuals, comprising 266 in group A and 192 in group B. The heterogeneity between the studies was significant ($I^2 = 82\%$, P < 0.001). After excluding Khoury's study, I^2 decreased from 83% to 32%, enabling the use of a fixed effect model. The result revealed no notable disparity in KOOS-pain scores between the groups [WMD = 0.38 (-3.62, 4.38), P = 0.85], as depicted in Figure 4.

Six studies [5, 6, 11, 13-15] reported KOOSsymptoms scores, with a total of 313 participants enrolled, comprising 155 in group A and 158 in group B. The heterogeneity between the studies was significant ($I^2 = 83\%$, P < 0.001). After excluding Khoury's study, I^2 decreased from 83% to 0%, enabling the use of a fixed effect model. The result revealed no notable

•			•				
Inclusion study	District	Sample	51	ugs injected oint cavity	Stem cell source	Follow-up time	Outcome index
		size	Group A	Group B		ume	Index
Bastos 2018 [5]	Brazil	18	MSCs	MSCs+PRP	Self/bone marrow	12 months	1
Bastos 2020 [6]	Brazil	30	MSCs	MSCs+PRP	Self/bone marrow	12 months	1
Estrada 2020 [7]	Argentina	62	MSCs	PRP	Self/adipose tissue	12 months	2
Lamo-Espinosa 2020 [8]	Spain	50	MSCs+PRP	PRP	Self/bone marrow	12 months	3
Dulic 2021 [9]	Serbia	145	MSCs	PRP	Self/bone marrow	12 months	123
Anz 2022 [10]	America	84	MSCs	PRP	Self/bone marrow	12 months	2 3
Baria 2022 [11]	America	58	MSCs	PRP	Self/adipose tissue	6 months	1
El-Kadiry 2022 [12]	Canada	39	MSCs	PRP	Self/adipose tissue	12 months	3
Zaffagnini 2022 [13]	Italy	108	MSCs	PRP	Self/adipose tissue	24 months	12
Khoury 2023 [14]	Qatar	50	MSCs	PRP	Self/adipose tissue	24 months	1
Baria 2024 [15]	America	49	MSCs	PRP	Self/adipose tissue	12 months	1

Table 2. The key features of the studies incorporate
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Note: ① Knee injury and osteoarthritis outcome score; ② International Knee Documentation Committee Subjective Knee Form; ③ Western Ontario and McMaster Universities osteoarthritis index.



Figure 2. Risk of bias graph.

disparity in KOOS-symptom scores between the groups [WMD = -1.48 (-5.90, 2.94), *P* = 0.51], as depicted in **Figure 5**.

Six studies [5, 6, 11, 13-15] reported KOOS-ADL scores, with a total of 313 individuals, comprising 155 in group A and 158 in group B. The heterogeneity among the studies was considerably notable ($l^2 = 81\%$, P < 0.001). After excluding Khoury's study, l^2 decreased from 81% to 0%, so a fixed effect model was used. The result revealed no notable disparity in KOOS-ADL scores between the groups [WMD = -2.36 (-6.87, 2.14), P = 0.30], as depicted in **Figure 6**.

Six studies [5, 6, 11, 13-15] reported KOOS-Sport/Rec score, with a total of 313 participants enrolled, comprising 155 in group A and 158 in group B. The heterogeneity between the studies was significant ($I^2 = 66\%$, P = 0.01). After excluding Khoury's study, I^2 decreased from 66% to 0%, so a fixed effect model was applied. The result revealed no notable disparity in the KOOS-Sport/Rec scores between the groups [WMD = -3.84 (-10.60, 2.92), P = 0.27], as depicted in **Figure 7**.

Six studies [5, 6, 11, 13-15] reported KOOS-QOL scores, with a total of 313 individuals, comprising 155 in group A and 158 in group B. The level of heterogeneity among the stud-

ies was considerably notable ($I^2 = 71\%$, P = 0.004). After excluding Khoury's study, I^2 decreased from 71% to 0%, so a fixed effect model was utilized, and the result revealed no notable disparity in KOOS-QOL scores between the groups [WMD = 0.09 (-5.48, 5.67), P = 0.97], as depicted in **Figure 8**.

Four studies [7, 9, 10, 13] reported the IKDC score, with a total sample size of 399 individuals, including 242 in group A and 157 in group B. The heterogeneity among the studies did not exhibit any significant homogeneity ($l^2 = 21\%$, P = 0.29), so a fixed effect model was applied, and the result revealed that group B exhibited a higher IKDC score compared to group A [WMD = 4.19 (2.57, 5.82), P < 0.001], as depicted in **Figure 9**.

The WOMAC score was reported in 4 studies [7-9, 12], with a combined sample size of 318 individuals, including 206 in group A and 112 in group B. The level of heterogeneity am-



Figure 3. Risk of bias summary.

ong the studies was not notable ($I^2 = 23\%$, P = 0.27), and a fixed effect model was applied. The result revealed no notable disparity in WOMAC scores between the two groups [WMD = 0.47 (-3.76, 4.70), P = 0.83], as depicted in **Figure 10**.

Publication bias assessment

For the analyses of KOOS-pain, KOOS-Symptoms, KOOS-ADL, KOOS-Sport/Rec, and KOOS-QOL score analysis, funnel plots were generated, as shown in **Figure 11A-E**. All the studies fell within the 95% confidence interval, however, asymmetry was observed at both ends of the distribution, suggesting the potential presence of publication bias.

Discussion

In 2015, the International Osteoarthritis Research Society redefined and standardized osteoarthritis, characterizing it as a condition

affecting the joints, marked by cellular strain and degradation of the extracellular matrix. This degradation is precipitated by micro and macro injuries that reactivate non-adaptive repair responses, including pathways involving inflammatory cytokines of the innate immune system [16]. Cartilage degeneration in osteoarthritis is due to the imbalance between the anabolism and catabolism pathways of chondrocytes, disrupting the homeostasis of the cartilage and leading to the destruction of the cartilage extracellular matrix and chondrocytes [17]. Therefore, effective prevention and treatment of osteoarthritis hinge on mitigating immune inflammation of cartilage and synovial tissue, curbing excessive apoptosis of chondrocytes, and promoting chondrocyte regeneration and cartilage repair.

In this analysis, 11 studies were integrated to assess the efficacy of MSCs and PRP in managing osteoarthritis. Our findings indicated no noticeable disparity in the five different dimensions of KOOS and WOMAC scores between the two groups. However, the IKDC score was found to be higher in the PRP group compared to the MSCs group, KOOS is mainly employed for the assessment of therapeutic effects on knee joint injury and osteoarthropathy. It contains five subscales, each can be applied separately. WOMAC primarily measures the degree of knee discomfort, mobility restriction, and motor function impairment. The findings indicated that the function and condition of the knee joint were equally improved after MSCs and PRP treatment. IKDC mainly focuses on changes in knee function and clinical outcomes, especially post-treatment evaluation and improvement of patient-reported symptoms and quantifiable indicators. These findings suggest that the knee function and condition following PRP treatment exhibit a modestly superior outcome compared to MSCs treatment.

The regeneration of chondrocytes may require local high concentrations of cytokines [18]. MSCs are present in various tissues and originate from non-hematopoietic adult stem cells of mesodermal origin (bone marrow, fat, synovium umbilical cord, etc.). The International Society for Cell Therapy demonstrate that MSCs have the following characteristics: First, they can attach to plastic; Second, the majority (over 95%) express CD73, CD90, and

Study	Selection	Comparability	Exposure/Outcome	Scorces
Estrada 2020 [7]	***	\$	**	6
El-Kadiry 2022 [12]	***	\$	**	6
Khoury 2023 [14]	***	\$	**	6

Table 3. Risk assessment of bias in cohort studies using NOS

NOS: Newcastle-Ottawa Scale.



Figure 4. Forest plot of KOOS-pain scores (after elimination). KOOS: knee injury and osteoarthritis outcome score.

	G	roup A		G	iroup B			Mean Difference		Mean D	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	1, 95% CI		
Zaffagnini 2022	9.5	16.1	53	9.7	17.6	55	48.3%	-0.20 [-6.56, 6.16]		-	•		
Khoury 2023	76.12	4.87	23	61.88	8.58	27	0.0%	14.24 [10.44, 18.04]					
Bastos 2020	61.6	22.5	16	60.5	17.6	14	9.4%	1.10 [-13.27, 15.47]			<u>├</u>		
Bastos 2018	54.5	22.2	9	63.8	15.3	9	6.3%	-9.30 [-26.91, 8.31]			+		
Baria 2024	71.8	20.5	26	76.4	20.2	23	15.0%	-4.60 [-16.01, 6.81]			+		
Baria 2022	75.37	19.45	28	76.38	17.87	30	21.0%	-1.01 [-10.64, 8.62]		_	-		
Total (95% CI)			132			131	100.0%	-1.48 [-5.90, 2.94]		•			
Heterogeneity: Chi ² =	= 1.33, df	= 4 (P =	0.86);	I ² = 0%					400		<u> </u>		
Test for overall effect	: Z = 0.66	6 (P = 0.	51)						-100	-50 Group A	U Group E	50 3	100

Figure 5. Forest plot of KOOS-symptoms scores (after exclusion). KOOS: knee injury and osteoarthritis outcome score.

	G	roup A		G	roup B			Mean Difference		Mean Dif	ference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, Fixed	, 95% CI		
Baria 2022	88.85	15.05	28	87.38	13.27	30	37.9%	1.47 [-5.85, 8.79]		-	-		
Baria 2024	83.7	18.4	26	84.5	17.1	23	20.5%	-0.80 [-10.74, 9.14]			_		
Bastos 2018	55.3	29.8	9	75	27.7	9	2.9%	-19.70 [-46.28, 6.88]			_		
Bastos 2020	58.4	27.5	16	66.3	27.4	14	5.2%	-7.90 [-27.59, 11.79]					
Khoury 2023	81.02	4.17	23	69.08	8.92	27	0.0%	11.94 [8.17, 15.71]					
Zaffagnini 2022	9.3	20.1	53	14.6	21.2	55	33.5%	-5.30 [-13.09, 2.49]			-		
Total (95% CI)			132			131	100.0%	-2.36 [-6.87, 2.14]		•			
Heterogeneity: Chi ² =	: 3.63, df	= 4 (P =	0.46);	l² = 0%					-100	-50 0		50	100
Test for overall effect	: Z = 1.03	(P = 0.	30)						-100	-50 Group A	, Group B		100

Figure 6. Forest plot of KOOS-ADL scores. KOOS: knee injury and osteoarthritis outcome score; ADL: activities of daily living.

CD105, while less than 2% express markers such as CD34, CD45, HLA-DR, CD14/CD11b, and CD79/CD19; Third, they can differentiate into osteocytes, chondrocytes, and adipocytes *in vitro*. Considering the causes of osteoarthritis and the inherent properties of MSCs, the potential therapeutic effects of MSCs on osteoarthritis may primarily involve autophagy, apoptosis, pro-inflammatory cytokines, and immune modulation. In the process of osteoarthritis, autophagy and apoptosis occur simultaneously, and the relationship between the two is com-

Efficacy of MSCs versus PRP in the therapy of osteoarthritis

	G	iroup A		G	roup B			Mean Difference		Mea	n Differend	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, F	ixed, 95% (CI	
Baria 2022	57.7	31.1	28	65.4	27.8	30	19.7%	-7.70 [-22.92, 7.52]		-			
Baria 2024	68.1	21.41	26	64.52	27.67	23	23.4%	3.58 [-10.41, 17.57]			-		
Bastos 2018	30.6	33.1	9	55	36.6	9	4.4%	-24.40 [-56.64, 7.84]			-+		
Bastos 2020	36.6	29.5	16	47.1	34.5	14	8.5%	-10.50 [-33.64, 12.64]					
Khoury 2023	66.52	4.38	23	57.59	5.94	27	0.0%	8.93 [6.06, 11.80]					
Zaffagnini 2022	12.6	29.6	53	15.3	24.1	55	43.9%	-2.70 [-12.90, 7.50]			-		
Total (95% CI)			132			131	100.0%	-3.84 [-10.60, 2.92]			•		
Heterogeneity: Chi ² =	3.26, df	= 4 (P =	= 0.52);	l² = 0%					-100	-50	<u> </u>	50	100
Test for overall effect	Z=1.11	I (P = 0.	27)						-100		p A Group		100

Figure 7. Forest plot of KOOS-Sport/Rec scores (after elimination). KOOS: knee injury and osteoarthritis outcome score; Sport/Rec: function in sport and recreation.

	Gi	oup A		G	iroup B			Mean Difference		Mean	Differend	се	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, Fix	ed, 95% (CI	
Baria 2022	68.1	21.1	28	63.71	21.97	30	25.3%	4.39 [-6.70, 15.48]					
Baria 2024	61.1	27.6	26	65	26.3	23	13.6%	-3.90 [-19.00, 11.20]		_	•		
Bastos 2018	38.3	29	9	45.3	26.7	9	4.7%	-7.00 [-32.75, 18.75]					
Bastos 2020	40.2	25.9	16	35.7	25.6	14	9.1%	4.50 [-13.96, 22.96]		-			
Khoury 2023	64.67	5.84	23	50	10.11	27	0.0%	14.67 [10.17, 19.17]					
Zaffagnini 2022	15.9	20.5	53	17.1	22.5	55	47.2%	-1.20 [-9.31, 6.91]			+		
Total (95% CI)			132			131	100.0%	0.09 [-5.48, 5.67]			♦		
Heterogeneity: Chi ² =	= 1.45, df	= 4 (P	= 0.83); I ² = 09	%				100	50	<u>+</u>		
Test for overall effect	: Z = 0.03	8 (P = 1	0.97)						-100	-50 Group	A Group	50 0 B	100

Figure 8. Forest plot of KOOS-QOL scores (after elimination). KOOS: knee injury and osteoarthritis outcome score; QOL: knee-related quality of life.

	G	roup A		G	roup B			Mean Difference		Меа	n Differend	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, I	ixed, 95%	CI	
Anz 2022	64.3	20.8	45	63.7	19.6	39	3.5%	0.60 [-8.05, 9.25]					
Dulic 2021	57.62	21.84	111	48.55	20.83	34	4.0%	9.07 [0.97, 17.17]					
Estrada 2020	64.2	3.6	33	59.8	3.4	29	87.0%	4.40 [2.66, 6.14]				-	
Zaffagnini 2022	12.8	19.2	53	13.2	17.6	55	5.5%	-0.40 [-7.35, 6.55]			-	_	
Total (95% CI)			242			157	100.0%	4.19 [2.57, 5.82]			•		
Heterogeneity: Chi ² =	3.79, df	= 3 (P =	0.29);	I ² = 219	6				+	-10	<u> </u>	10	20
Test for overall effect:	Z = 5.05	ő (P ≤ 0.	00001)						-20		ip A Group		20

Figure 9. Forest plot of IKDC scores. IKDC: International Knee Documentation Committee Subjective Knee Form.

	G	roup A		G	iroup B			Mean Difference		Me	ean Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV	Fixed, 95%	CI	
Anz 2022	19.4	16.2	45	16.8	16.9	39	35.4%	2.60 [-4.51, 9.71]			- + -		
Dulic 2021	24.23	20.91	111	31.06	23.34	34	23.3%	-6.83 [-15.59, 1.93]					
El-Kadiry 2022	75.12	16.87	26	70	13.11	13	19.3%	5.12 [-4.52, 14.76]			- + =		
Lamo-Espinosa 2020	23	16.6	24	22.3	15.8	26	22.1%	0.70 [-8.30, 9.70]			+		
Total (95% CI)			206			112	100.0%	0.47 [-3.76, 4.70]			•		
Heterogeneity: Chi ² = 3.	•	•	<i></i>	= 23%					-100	-50		50	100
Test for overall effect: Z	= 0.22 (F	r = 0.83)	,							Gr	oup A Group	bВ	

Figure 10. Forest plot of WOMAC scores. WOMAC: Western Ontario and McMaster Universities osteoarthritis index.

plex. Autophagy protects chondrocytes from apoptosis, which may be related to cartilage differentiation. MSCs can delay the progression of osteoarthritis by enhancing autophagy, reducing chondrocyte apoptosis, and regulating cartilage matrix enzymes [19, 20]. In addition, MSCs exert anti-apoptotic effects by releasing transforming growth factor- β , vascular endothelial growth factor, and fibroblast growth factors. MSCs can reduce the liberation of substances that cause inflammation including tumor necrosis factor- α (TNF- α), interleukin-1,



Figure 11. Funnel plots. A: KOOS-pain based analysis; B: KOOS-Symptom based analysis; C: KOOS-ADL based analysis; D: KOOS-Sport/Rec based analysis; E: KOOS-QOL based analysis. KOOS: knee injury and osteoarthritis outcome score; ADL: activities of daily living; Sport/Rec: function in sport and recreation; QOL: knee-related quality of life.

and interleukin-6, and increase the production of anti-inflammatory mediators [21]. MSCs can both suppress and promote inflammatory factors, for example, TNF- α and interleukin-1 β , which are implicated in cartilage degeneration. chondrocyte death, and degradation of the cartilage matrix, as well as hinder the synthesis and regeneration of new cartilage. M1 macrophages are prone to secrete these pro-inflammatory factors [22]. Compared with M1, M2 macrophages can release molecules with antiinflammatory properties, including interleukin-10, antagonists for interleukin-1 receptors, chemokines, as well as chondrogenic cytokines like transforming growth factor- β and insulin growth factor, which promote chondrocyte proliferation and cartilage repair. MSCs facilitate the transition of gene expression indicators from M1 to M2, promoting macrophage polarization to M2 phenotype, enabling macrophages to exhibit anti-inflammatory properties, up-regulate CD206, enhance the production of interleukin-10 while decreasing the release of interleukin-1 β , through the coordination and effective activation of multiple cell types to achieve effective cartilage regeneration [23, 24]. Thus, while numerous studies have concluded that MSCs can repair joint surface damage, the functionality of MSCs is heavily depend on the local microenvironment of the joint. Disruption in the dynamic equilibrium within the joint and subsequent inflammatory and apoptotic conditions can significantly impact the proliferation and tissue differentiation of MSCs. Zhao et al. [25] conducted a meta-analysis encompassing six studies, revealing that compared to solitary MSCs, co-administration of MSCs with PRP yielded superior outcomes in ameliorating pain and enhancing joint function among patients with knee osteoarthritis. One potential explanation for this phenomenon is that adjunctive PRP administration may enhance the intra-articular microenvironment, thereby fostering the proliferation and differentiation of MSCs. The role of PRP depends on the ability of high-concentration platelets to release various growth factors and bioactive proteins with super-physiological amounts, such as insulin-like growth factor, vascular endothelial growth factor, transforming growth factor-β, fibroblast growth factor, plateletderived growth factor, connective tissue growth factor, and epidermal growth factor. These growth factors facilitate the mobilization, proliferation, and differentiation of autologous tissue cells and enhance the tissues repair [26, 27]. In contrast, the differentiation process of MSCs is relatively complex and time intensive. Therefore, PRP treatment may have a more direct and significant effect in improving joint function, resulting in a higher score on the IKDC score.

MSCs have garnered significant attention in the field of regenerative medicine, and their potential application in treating osteoarthritis is still at an exploratory stage. Concurrently, PRP represents another non-surgical treatment option that also demonstrates promising potential. This study presents scientific evidence for evaluating the efficacy of these two emerging therapies through a comprehensive meta-analysis, addressing existing research gaps. Additionally, the study incorporates a multidimensional scoring system to thoroughly assess the impact of both treatments on patients' pain, symptoms, daily activities, mobility function, and quality of life, thereby providing valuable insights for clinical decision-making. Nevertheless, there are still several limitations: (1) The studies analyzed have a small sample size, potentially affecting stability and reliability of the results. (2) Differences in puncture point, injection dose, preparation process and course of treatment along with inconsistent follow-up time have inevitably influenced the outcomes. (3) The absence of comprehensive blinding descriptions in the studies introduces a risk of bias, necessitating cautious interpretation of the results. Hence, additional studies of substantial size and superior quality are needed to reinforce the meta-analysis and establish more persuasive findings.

In summary, the effectiveness of MSCs and PRP treatments are comparable in terms of KOOS and WOMAC scores for osteoarthritis within 12 months after treatment. However, PRP treatment demonstrates higher IKDC score than that of MSCs. Overall, the shortterm effectiveness of intra-articular administration of PRP for managing osteoarthritis is slightly better than that of MSCs.

Disclosure of conflict of interest

None.

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