REVIEW ARTICLE

Efficacy and safety of mesenchymal stem cell injections for knee osteoarthritis: A systematic review and meta-analysis

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Background: There have not been any clear studies on the use of mesenchymal stem cells (MSCs) to treat osteoarthritis (OA) in the knee. **Materials and Methods:** This study investigates the effects of different MSC dosages on pain alleviation in individuals with OA in the knee by conducting a meta-analysis of existing randomized controlled trials. Electronic resources such as Google Scholar, PubMed, Cochrane Library, and Web of Science were searched up until June 2023. Treatment effect sizes were computed using the knee osteoarthritis outcome score (KOOS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the Knee Society Score (KSS). Random or fixed effect models were applied to aggregate the data. We performed a subgroup analysis according to dosage level. The heterogeneity of the research was investigated using the Chi-square test and the I2 index. **Results:** The meta-analysis included 26 studies with a total sample size of 739 patients. A significant reduction in pain was observed 1 year and 2 years following the injection of MSCs into the injured joint, as indicated by the Visual Analogue Scale, WOMAC, KOOS, and KSS indexes ($P < 0.05$). Patients on MSCs reported much reduced pain after 1 and 2 years compared to the control group ($P < 0.05$). Subgroup and meta-regression analyses revealed no statistically significant variations in the effectiveness of MSC dosage ($P < 0.05$). The studies did not report any adverse effects. **Conclusion:** Different dosages of MSCs had the same pain-relieving effects on patients with OA in the knee. MSC injections were safe and beneficial in such cases.

Key words: Knee, mesenchymal stem cells, meta-analysis, osteoarthritis, safety, treatment outcome

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INTRODUCTION

A chronic joint illness called osteoarthritis (OA) is typified by secondary osteogenesis and articular cartilage degradation. Millions of individuals worldwide suffer from OA, a widespread joint condition that is more common in those over 60 years.[1] Although several treatment options are available for OA, including exercise, medication, and surgery, none of them can promote the regeneration of degenerated tissue.[2] Mesenchymal stem cells (MSCs) have emerged as a promising treatment option for OA due to their ability to differentiate into chondrocytes and modulate the immune system.[2,3] MSCs have become the most extensively explored new therapeutic agents for OA.[4] OA is a destructive joint disease, in which the synovial joints are involved, and the joint cartilage is gradually destroyed.[5] There is a change in the function of the whole joint, including the meniscus of the knee, the ligament around the joint, and the bone under the cartilage.[6] The risk factors that cause this complication include age, gender,[7] genetic,[8] obesity,[9] previous injury,[10] and sport.[11] OA disorder is common in the United States, it occurs in older, and in terms of gender, it is more common in women than men. Pain, joint swelling, and synovitis are clinical symptoms of the disease.[12] One of the main gold standards for its diagnosis is tissue biopsy,[13] but other techniques such

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as magnetic resonance imaging,[14] radiography are useful for diagnosis; radiographic findings include joint space reduction, osteophysis, subcartilage, sclerosis, and cyst formation.[15]

Treatment methods include nonsteroidal anti-inflammatory drugs (NSAIDs). The joint injection method is corticosteroid or hyaluronic acid (HA). Regarding the mentioned treatments, NSAIDs have high toxicity; on the other hand, HA injection has little effect and lasts for about 6 months.[16,17] On the other hand, corticosteroid injection damages the cartilage and makes the person susceptible to joint replacement.[18] Therefore, for this cartilage defect in patients with OA, an alternative must be found and it must be a cell source.[19] MSCs are multipotent cells that can differentiate into various cell types, including chondrocytes, which are the cells that produce cartilage.[20] Although it has been suggested that intra-articular MSC injection is a potential therapy option for knee OA (KOA), its effectiveness is still rather restricted.[21]

The source of stem cells is bone marrow, adipose tissue, umbilical cord, amniotic fluid, dental pulp, synovial tissue, peripheral blood, and skeletal muscle.[22] Stem cells in adults have different sources; the most common is the bone marrow, which is removed locally or systemically. Bone marrow has advantages over other sources, including it provides a high concentration of stem cells in a smaller volume, is easy to access, does not require a central venous catheter, and eliminates apheresis, which is a troublesome procedure, among its other benefits, we can mention their capacity to regenerate damaged cartilage and reduce the pain of patients. As previously said, there are various techniques to treat OA in the knee; however, injecting MSCs is the most effective way.[23] The following are the causes of this superiority: (1) self-renewal, (2) essential to preserving the cartilage in its typical condition, (3) chemotaxis to the cartilage-damaged area, (4) promoting cartilage cell production and multiplication.[24] Tuberculosis adipose-derived MSCs (AD-MSCs), endothelial progenitor cells, endothelial cells, macrophages, smooth muscle cells, lymphocytes, pericytes, and prefats are the sources from which MSCs are derived. Compared to bone marrow-derived MSCs, the activity of adipose-derived stromal vascular fraction (SVF) stem cells is three times higher. However, the effectiveness and safety of MSC injection for KOA treatment are still relatively new and have yet to gain popularity.[1] The purpose of the present meta-analysis and systematic review is to assess the safety and effectiveness of MSC intra-articular injections in the treatment of KOA. Randomized controlled trials (RCTs) evaluating the effectiveness and safety of MSC intra-articular injections compared to placebo are included in the study.[4,20,25] The review assesses the various MSC sources, including bone marrow, umbilical cord, and AD-MSCs, that are utilized to treat OA in the knee.[26-28]

The objective of this study was to pool evidence about the efficacy and safety of injecting bone marrow and adipose tissue MSCs to decrease KOA patients' pain using a systematic review and meta-analysis.

MATERIALS AND METHODS

Protocol and registration

The PRISMA guideline and the published protocols of the Cochrane Collaboration were followed throughout the data analysis process and inclusion criteria of each study.[29,30] The study was not registered in PROSPERO.

Eligibility criteria

The inclusion criteria were established to identify RCTs that investigated KOA patients and the injection of bone marrow or AD-MSCs into the knee joint. It was necessary to conduct studies to quantify certain outcomes associated with KOA and to compare the MSCS intervention with standard therapy. On the other hand, exclusion criteria made sure that reviews, irrelevant publications, animal research, and studies without a control group were left out. We select the studies with follow-ups of at least a year. The PICO criteria were used to select the following eligibility requirements for our study:

- P: Participants: Adults with OA in their knees I: Interventions: MSC injection
- C: Comparisons: Placebo or alternative treatments for OA in the knee, as well as trials without a control group, animal studies, review articles, and other publications (such as *in vitro* stem cell injection) were disregarded. O: The safety and effectiveness of injecting MSCs. The outcomes measured include patient-reported outcome measures (PROMs) such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the knee Injury And Osteoarthritis Outcome Score (KOOS), Knee Society Score (KSS), and the Visual Analog Scale (VAS) score, as well as adverse events (AEs).[4,25]

Information sources

To find relevant studies, a search was conducted across electronic databases such as PubMed, Embase, Scopus, and the Cochrane Library. In addition, we searched across conference proceedings and clinical trial registries for ongoing or unpublished research. We also conducted a manual search of relevant article reference lists to find any other research that would have needed to be included in the electronic search.

Search strategy

The search plan was created after consulting a medical librarian. It contained terms and medical subject headings (MeSH) pertaining to bone marrow, KOA, adipose tissue, pain, MSCs, and RCTs. Treatment outcome, safety, KOA, analgesia, MSCs, and meta-analysis were the terms in the MeSH. Only studies published in English were included in the search. The search continued till July 2023.

Selection process

Based on the predetermined criteria, two reviewers independently examined the titles and abstracts of every study that was found to be eligible. For studies that either met the eligibility requirements or for which the title and abstract did not provide sufficient information to assess eligibility, full-text articles were obtained. Any differences in the full-text articles' eligibility were determined by two reviewers working separately, and a third reviewer was consulted to settle any disputes.

Data collection process

Study characteristics (author, year of publication, study design, etc.), participant characteristics (age, sex, and KOA severity), intervention characteristics (kind of MSCs, dose, and frequency), comparison characteristics (placebo or other interventions), and outcome data (VAS, WOMAC, KSS, KOOS index, mean, and standard deviation (SD) before and after intervention) were among the information that was extracted.

Study risk of bias assessment

Reporting bias was assessed using the PRISMA 2020 reporting guideline.[30]

To assess the risk of bias within the included studies, various factors were considered, including randomization methods, allocation concealment, blinding of participants and outcome assessors, and other pertinent aspects that could potentially influence the validity of the findings.[31] The Cochrane risk of bias tool[31] was utilized to evaluate the bias risk of the included studies. A pair of reviewers will separately evaluate each study's potential for bias.

Statistical analysis

The main outcome of the study was pain reduction in KOA patients. Pain reduction measure by Analog Scale (VAS), (WOMAC), Knee Society Score (KSS), and (KOOS). Authors' names, the year of publication, sample sizes, MSCs injection dosage and delivery, and the length of follow-up are among the details. A standard mean difference (SMD) served as the primary effect size (ES). The mean and SDs of the mentioned criteria were collected from articles for the treatment and control groups. In certain research studies, the median and interquartile range (IQR) are presented instead of the mean and SD. In these cases, the mean was estimated using the median, and the SD was calculated using the formula SD = IQR/1.35. SMD was contrasted before and after treatment between MSCs and control groups, and the SMD was pooled among subgroups. When there was low heterogeneity among studies, the fixed-effect inverse variance model was used to pool the results of studies, versus when heterogeneity among studies was significant, we used random effect models. I^2 and H^2 statistics were used to show heterogeneity. An I^2 of < 25% is usually viewed as low heterogeneity, between 25% and 50% as moderate, and over 50% as high heterogeneity. The significance of the H^2 statistic was checked with the Z test. Subgroup analysis was done according to the dosage of MSCs. The findings were presented in graphical format, allowing clear visualization of the results. Data were analyzed using Stata Corp (2017) Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. STATA Ver. 15. P <0.05 was considered statistically significant.

RESULTS

Study selection

A total of 2376 relevant papers were discovered through database searches, including 1065 in PubMed, 605 in Google Scholar, 496 in Cochrane, and 210 in Web of Sciences; 70 items were discovered through reference checking following the removal of 790 duplicate articles, and 1656 articles underwent screening and review. One thousand four hundred fifty articles out of 1656 were eliminated after it was determined the title was irrelevant. A total of 206 articles were evaluated, of which 180 were left due to the lack of a control group, or work on animals. The number of studies was selected based on the number of doses entered. Seven papers worked on adipose tissue, another eight on MSC-derived bone marrow, and one study on cord blood. Because our study is based on the injection dose of MSCs, our final study consisted of 26 because our investigation is predicated on the injection dosage of MSCs. Twelve of these investigations used low dosages, seven used high doses, and four used unknown doses. Figure 1 shows the PRISMA flow diagram for research selection. Table 1 shows the overall features of the studies that were part of the meta-analysis. Our final study consisted of 26 because our investigation was predicated on the injection dosage of MSCs. Twelve of these investigations used low dosages, seven used high doses, and four used unknown doses. Figure 1 shows the PRISMA flow diagram for research selection. Table 1 shows the overall features of the studies that were part of the meta-analysis.

Table 2 lists the methodological quality of the identified research. There was not a single included study with a high enough overall risk of bias to be removed from the analysis.

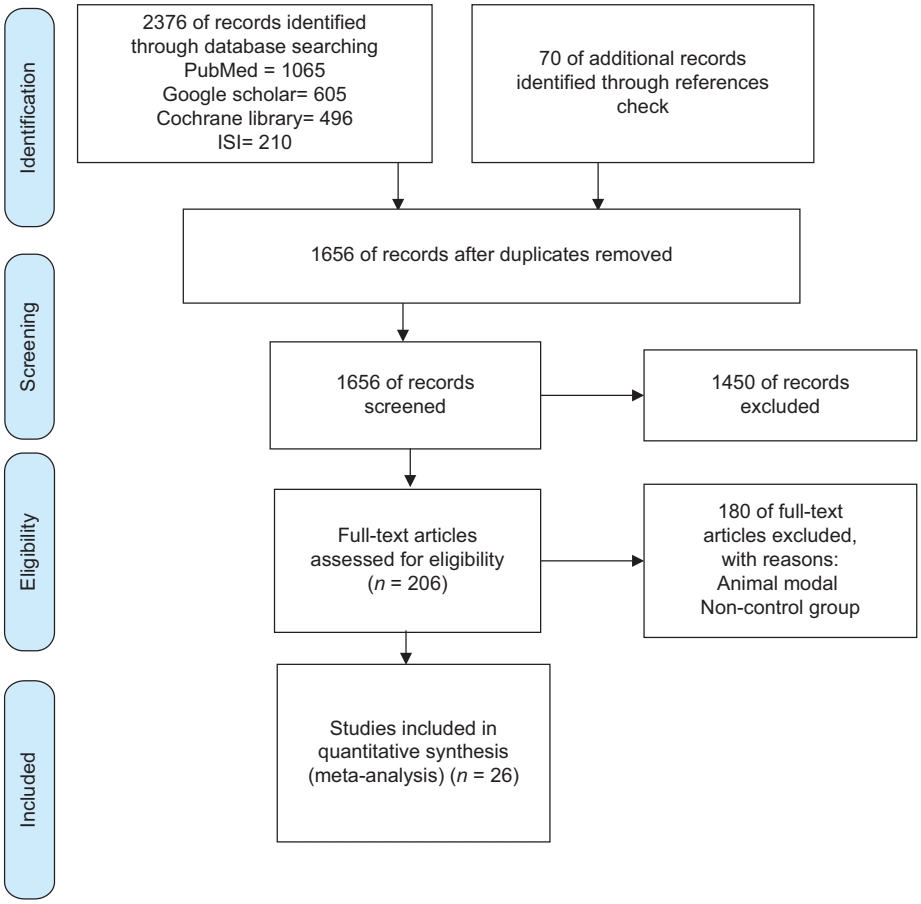

Figure 1: PRISMA flow diagram included studies

Table 1: Characteristics of included studies

Reference	First author	Year	Country	Source	Dose	Sample size (case/control)	Control group	Index	Follow-up (months)
1	Vega *et al.*[32]	2015	Spain	BM	Low	15/13	15	VAS, WOMAC	12
2	Kuah *et al.*[33]	2018	Australia	AD	Low, high	20		VAS, WOMAC	12
3	Lamo-Espinosa *et al.*[24]	2016	Spain	BM	Low, high	20	10	VAS, WOMAC	12
4	Garza *et al.*[34]	2020	USA	AD	Low, high	26	13	WOMAC	12
5	Bastos *et al.*[35]	2020	Brazil	BM	Low	47		KOOS	12
6	Tran *et al.*[36]	2019	Taiwan	AD	Low	18	15	VAS, WOMAC	24
7	Spasovski *et al.*[37]	2018	Serbia	AD	One-dose	9		VAS, KSS	18
8	Vangsness *et al.*[38]	2014	USA	BM	Low, high	55		VAS, KSS	24
9	Lee *et al.*[39]	2012	Singapore	BM	One-dose	35		VAS	24
10	Jo *et al.*[40]	2017	Seoul	AD	Low, medium, high	18		WOMAC, VAS, KSS, KOOS	24
11	Orozco *et al.*[41]	2013	Spain	BM	One-dose	12		WOMAC, VAS	12
12	Pers *et al.*[42]	2016	Ireland	AD	Low, medium, high	18		WOMAC, VAS	12
13	Kim *et al.*[43]	2022	Seoul	AD	One-dose	11		VAS, WOMAC	5-year
14	Chahal *et al.*[44]	2019		BM	Low	13		WOMAC, KOOS	12
15	Garay-Mendoza[45]	2018		BM	Low	32		KSS, KOOS	12
16	Song[46]	2020	Seoul	Blood	Low, medium, high	128		VAS, WOMAC	24

VAS=Visual Analogue Scale; WOMAC=Western Ontario McMaster Universities Osteoarthritis Index; KOOS=Knee osteoarthritis outcome score; KSS=Knee scale score; BM=Bone marrow; AD=Adipose-derived

Efficacy outcomes

Western Ontario McMaster Universities Osteoarthritis Index for pain at 12 months

There were eight studies that reported functional results at 1-year WOMAC score. Among the included studies, there was a significant heterogeneity (Q[16] =128.9, I^2 = 95.04%, P = 0.000). For analysis, the random-effect model was thus applied. After a year of treatment, the WOMAC

Table 2: The methodological quality of the included studies

	Random sequence (selection bias)	Allocation concealment	Blinding of particle	Blinding out come	Incomplete outcome	Selective reporting	Other bias
Vega	✔	✔	✔	✔	×	×	
Kevin lee	×	✔	✔	✔	×	×	
Thomas	✔	✔	✔	✔	×	×	
Chris jo	✔	✔	✔	✔	×	×	
Lluis	✔	✔	✔	✔	×	×	
Kang	✔	✔	✔	✔	×	×	
Dusko	✔	✔	✔	✔	×	×	
Yves	✔	✔	✔	✔	×	×	
Tran	×	✔	✔	✔	×	×	
Bastos	✔	✔	✔	✔	×	×	
Lamo	✔	✔	✔	✔	×	×	
Garza	✔	✔	✔	✔	×	×	
Chahal	✔	✔	✔	✔	×	×	
Gancars	✔	✔	✔	✔	×	×	
Seobsong	✔	✔	✔	✔	×	×	
Kuah	✔	✔	✔	✔	×	×	

✔: Yes, ×: No

score changed significantly [SMD = −2.39, 95% confidence interval (CI) (−3.19–−1.59), Figure 2a]; in the control group, the score was SMD =−0.95, 95% CI (−1.23–−0.68) [Figure 2b], and the CI for SMD did not overlap, indicating that MSC efficacy in pain reduction was significantly better ($P < 0.05$). Figure 2a Q (3) =0.74, $P = 0.86$, and the Chi-square test (test of group difference) indicates that there was no statistically significant difference between the four groups (low, medium, high dose, and unknown dose).

Western Ontario McMaster Universities Osteoarthritis Index for pain at 24 months

At 2 years, functional results with WOMAC scores were reported in 17 clinical trials. The included studies showed significant heterogeneity (Q[10] =44.66, I^2 = 90.25%, $P = 0.000$). For analysis, the random-effect model was thus applied. After 2 years of treatment, there was a significant improvement in the WOMAC score (SMD = −2.15, 95% CI [−2.77–−1.54], $P = 0.000$). Figure 3 Q (3) =5.57, $P = 0.13$, the Chi-square test (test of group difference) demonstrates that there was no statistically significant difference between the four groups (low, medium, high doses, and unknown doses).

Visual Analog Scale for pain at 12 months

Ninety studies reported functional outcomes with VAS score at 1 year. There was a significant heterogeneity among the included studies (Q[18] =174.59, I^2 = 94.64%, $P = 0.000$). Hence, the random-effects model was used for analysis. Change in VAS score was significant after 1 year of treatment (SMD = −2.46, 95% CI [−3.16–−3.16–−1.76], $P = 0.000$). The Chi-square test (test of group difference) shows that there was no significant difference among four groups (low, medium high dose, and unknown) Q[3] =0.23, $P = 0.97$, [Figure 4a].

Visual Analog Scale for pain at 24 months

There were nine studies that reported functional results at 2 years with VAS scores. The included studies showed significant heterogeneity (I^2 = 93.76%, $P = 0.000$). For analysis, the random-effects model was thus applied. After a year of treatment, there was a substantial change in the VAS score (SMD = −2.48, 95% CI [−3.25–−1.71], $P = 0.000$). Q[3] =2.03, $P = 0.57$, the Chi-square test revealed no statistically significant difference between the four groups (low, medium, high doses, and unknown dose). Significant heterogeneity between studies was revealed by the heterogeneity test (Q[8] =77.23, $P = 0.000$, [Figure 4b]).

KSS for pain at 12 months

Functional results with KSS score at 1 year were reported in seven trials. The selected studies showed significant heterogeneity (Q[6] =136.40, I^2 = 98.01%, $P = 0.000$). Thus, for analysis, the random-effects model was employed. After a year of treatment, there was not a significant improvement in the KSS score (SMD = 2.67, 95% CI [−0.15–5.50], $P > 0.05$). The four groups (low, medium, high doses, and unknown dose) did not significantly differ from one another, according to the Chi-square test (test of group difference) Q[3] =1.79, $P = 0.62$, [Figure 5a].

KSS for pain at 24 months

Five studies reported functional outcomes with KSS scores at 2 years. Significant heterogeneity was among the included studies (Q[4] =66.98, I^2 = 97.39%, $P < 0.001$). Hence, the random-effects model was used for analysis.

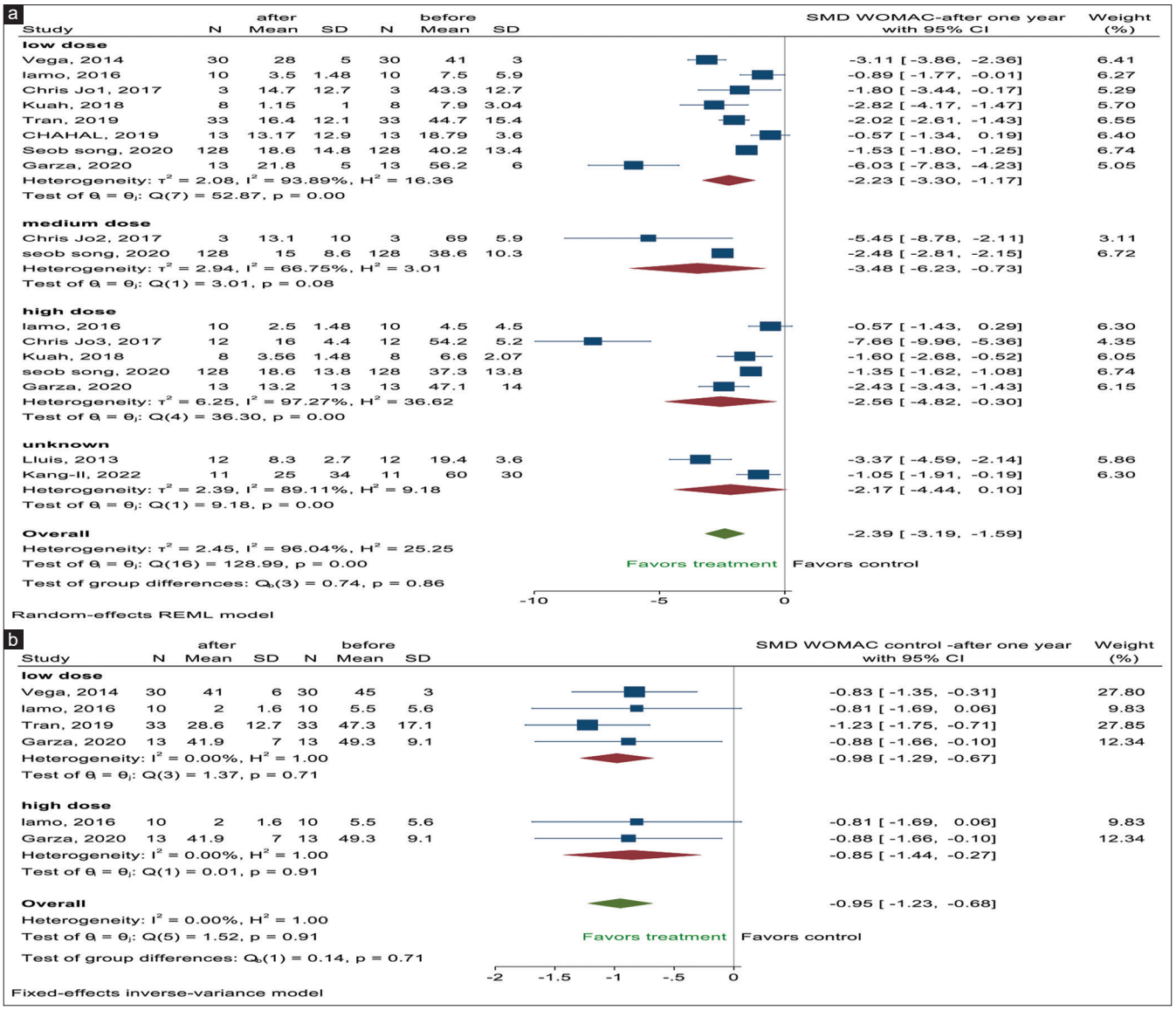

Figure 2: Comparison of WOMAC score before intervention and one years after intervention (a) intervention group, (b) control group

The KSS score change was insignificant after 2 years of treatment (SMD = 2.15, 95% CI [−0.99–5.30], P = 0.595) years. The Chi-square test (test of group difference) shows that there was no significant difference among the four groups (low, medium-high dose, and unknown dose), Q[2] = 1.05, P = 0.59, [Figure 5b].

Knee injury and osteoarthritis outcome score for pain at 12 months

At 1 year, functional outcomes with KOOS score were reported in six studies. The selected studies showed significant heterogeneity (Q[5] =58.23, I^2 = 97.31%, P = 0.000). For analysis, the random-effects model was thus applied. After a year of treatment, there was a substantial change in the KOOS score (SMD = 2.30, 95% CI [0.18–4.42], P = 0.000). Four groups (low, medium, high dose, and unknown dose) had a significant difference, according to the Chi-square test (test of group difference) Q[2] =23.53, P = 0.97 [Figure 6a].

Knee injury and osteoarthritis outcome score for pain at 24 months

At 2 years, functional outcomes with KOOS score were reported in five trials. The included studies showed significant heterogeneity (Q[4] =20.69, I^2 = 84.96%, P = 0.000). For analysis, the random-effects model was thus applied. After 2 years of treatment, there was a substantial change in the KOOS score (SMD = 2.79, 95% CI [0.99–4.59], P = 0.000). Q[2] =0.49, P = 0.78 [Figure 6b]; the Chi-square test (test of group difference) reveals that there was no significant difference between the four groups (low, medium-high dose, and unknown dose).

Publication bias

A funnel plot for publishing bias is displayed in Figure 7, with most funnel plots displaying symmetry.

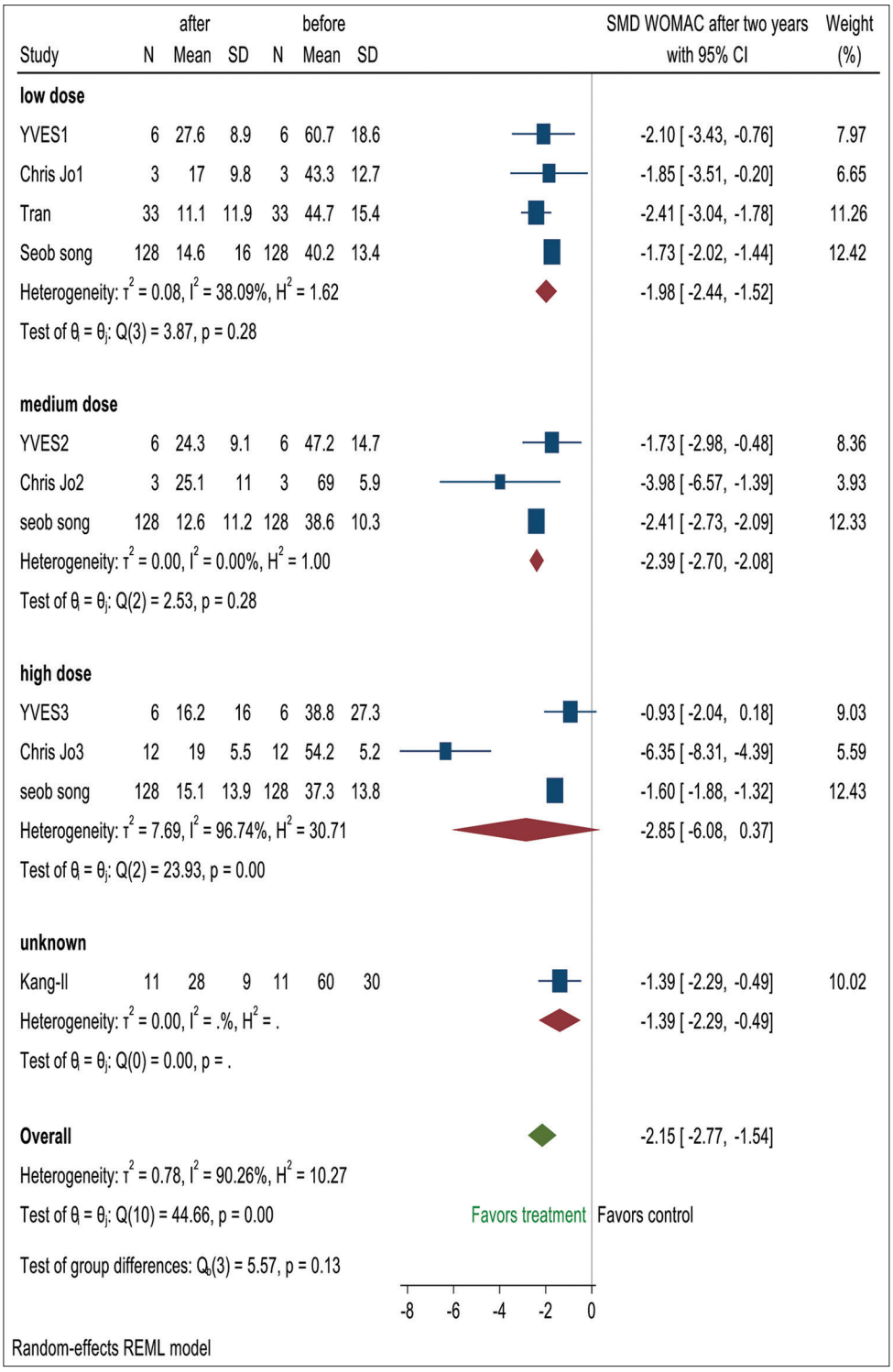

Figure 3: Comparison of Western Ontario and McMaster Universities Osteoarthritis Index score before intervention and 2 years after intervention

Safety

There were no notable adverse effects, such as tumors or death. Even if there were some reported complications, they were either self-treated or resolved.

Subgroup analysis

The effectiveness of the four MSC doses was not different significantly, according to subgroup analysis according to dose [Figures 2-6].

Publication bias

Publication bias was analyzed and investigated using Eger's regression test for meta-analysis of the efficacy and safety of MSCs injection in managing OA. All studies

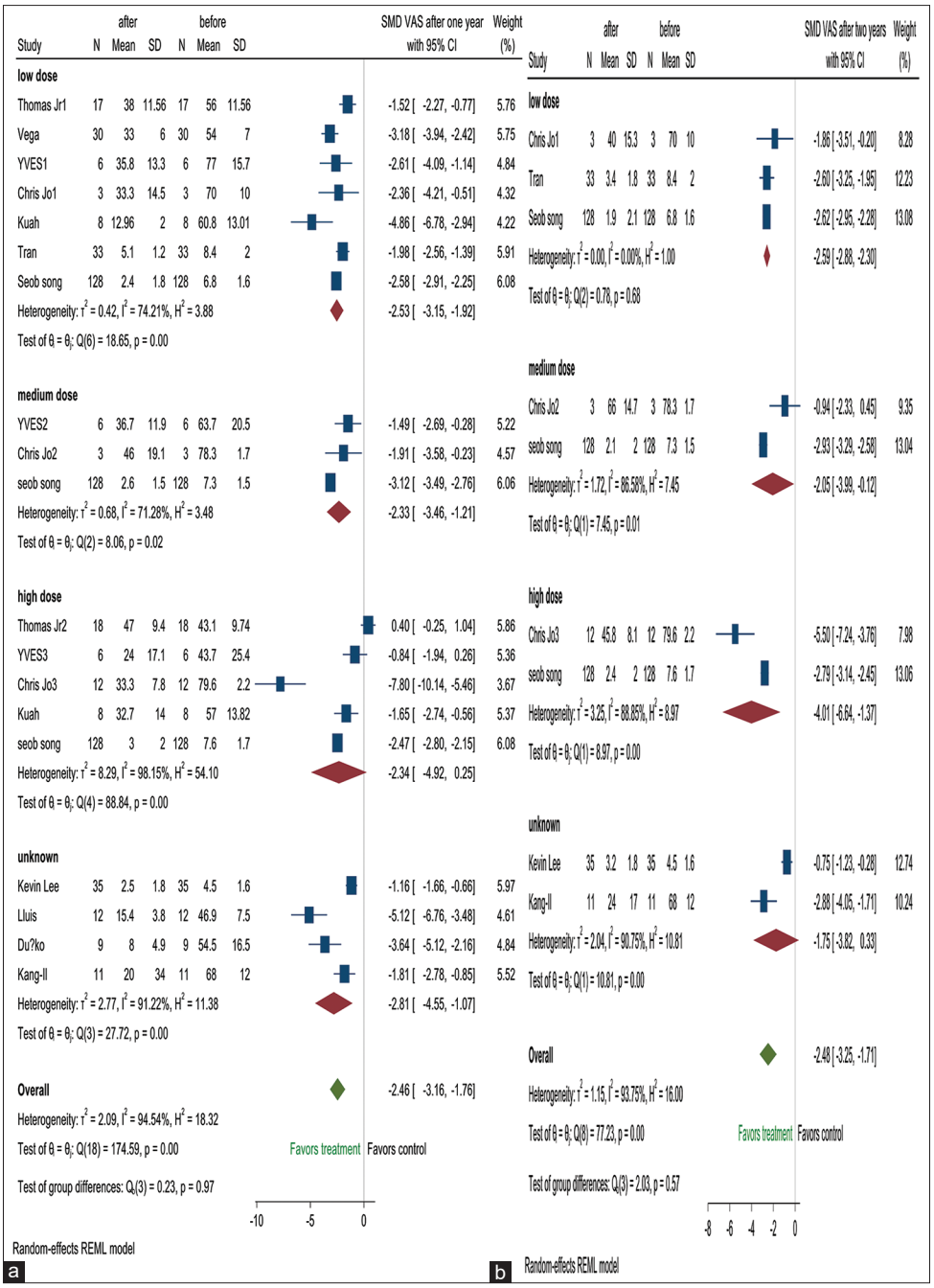

Figure 4: Visual Analogue Scale (VAS) scores after intervention compared to before intervention (a) One year, (b)Two years

were within the 95% CI and equally distributed on the CI, indicating minimal publication bias [Figure 7a-g]. The nonparametric analysis estimated that 14 studies were probably not published, and by evaluating the ES of these 14 unpublished studies and combining this estimate with the estimate of real data, it can be said that the estimated effect size does not change. Hence, we can be confident in the results and say that MSCs have effectively reduced pain [Table 3]. The Association SMD with WOMAC index with source of MSC and dose MSC after 1 and 2 years from follow-up is shown in Figure 8. To avoid putting many figures in the article, we used multivariate meta-regression. Multivariate meta-regression showed that according to WOMAC and VAS indexes, there was no significant association between dose and source MSCs with efficacy MSCs ($P > 0.05$, [Table 4]), but according to KSS, after 1 year source of MSCs an affected MSCs efficacy ($P < 0.05$, [Table 4]).

Sensitivity analysis

To check if an individual study can change the overall results, We used metaninf commend in STATA, the results

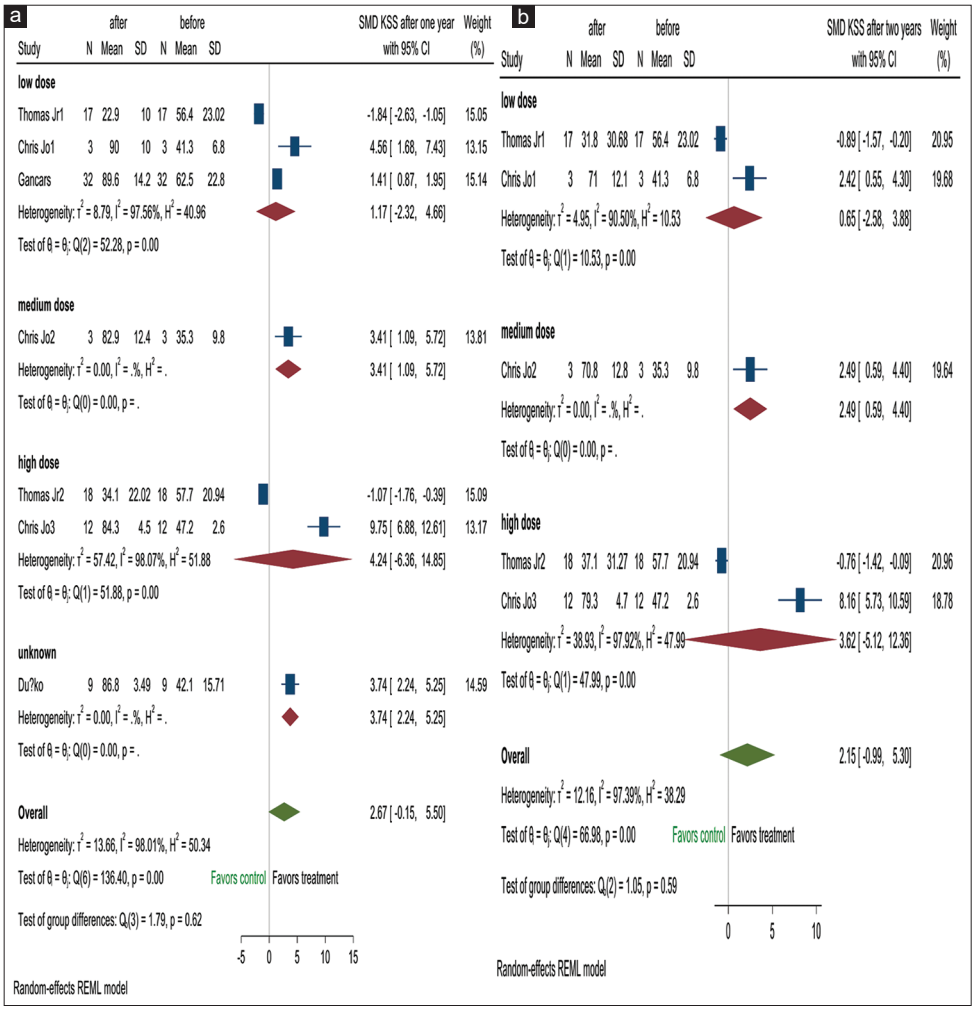

Figure 5: Pre intervention and 1-and 2-year post intervention Knee Society score (KSS) score comparison (a) One year, (b) Two years

Table 3: Comparison between observed and observed + imputed estimates of effects sizes

Imputation unpublished study	Studies	Theta	95% CI
SMD WOMAC after 1 year	Observed	1.77	1.63–1.91
	Observed + imputed	1.63	1.49–1.76
SMD WOMAC after 2 years	Observed	1.9	1.76–2.06
	Observed + imputed	1.88	1.73–2.03
SMD VAS after 1 year	Observed	2.77	2.13–3.41
	Observed + imputed	2.29	2.08–2.37
SMD VAS after 2 years	Observed	2.49	2.32–2.66
	Observed + imputed	2.49	2.32–2.66
SMD KOOS after 1 year	Observed	1.10	0.80–1.40
	Observed + imputed	1.10	0.80–1.40
SMD KOOS after 2 years	Observed	2.36	1.69–3.06
	Observed + imputed	2.36	1.69–3.06
SMD KSS after 1 year	Observed	0.44	0.09–0.80
	Observed + imputed	0.07	0.26–0.41

CI=Confidence interval; WOMAC=Western Ontario McMaster Universities Osteoarthritis Index; KOOS=Knee osteoarthritis outcome score; KSS=Knee scale score; VAS=Visual Analogue Scale; SMD=Standard mean difference

show there were not influence studies to change overall results [Figures 9 and 10].

DISCUSSION

The study's findings demonstrated that, as compared to both the control group and the patients' pretreatment levels, MSC injections significantly decreased knee pain in OA patients after 1 and 2 years of injection. MSCs are multipotent cells that have the ability to differentiate into diverse cell types, such as cartilage-producing chondrocytes.[10] It has been shown that KOA may be successfully treated with intra-articular injection of MSCs.[47]

Multidisciplinary clinical trials (RCTs) have assessed the effectiveness of intra-articular MSC injections in the treatment of KOA. A systematic review and meta-analysis of six controlled clinical trials found that MSCs combined with platelet-rich plasma (PRP) had no significant effect on the reduction of the VAS score in patients with KOA compared with the control, HA, or PRP alone at 3 months after treatment. However, compared to the control, MSCs + PRP was more successful in lowering the VAS score 6 and 12 months after treatment. When compared to

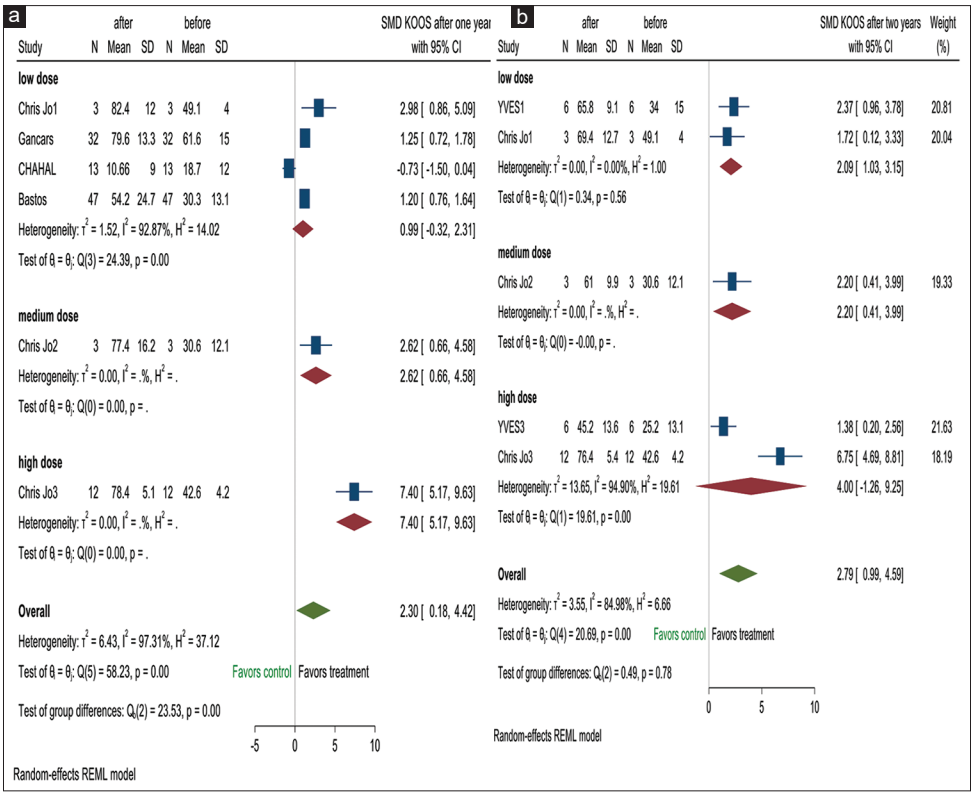

Figure 6: Comparison of the knee osteoarthritis outcome score before and after the intervention at 1 and 2 years (a) One year, (b)Two years

Table 4: Multivariate meta-regression dose and source of mesenchymal stem cells with mesenchymal stem cells efficacy

	Covariates	Coefficient	SE	*Z*	*P*
WOMAC					
1-year	Dose	0.04	0.385	0.12	0.906
	Source	0.611	0.519	1.18	0.239
2-year	Dose	0.017	0.397	0.04	0.966
	Source	0.233	0.428	0.55	0.586
VAS					
1-year	Dose	0.020	0.333	0.06	0.952
	Source	0.004	0.448	0.01	0.992
2-year	Dose	0.012	0.406	0.03	0.976
	Source	0.213	0.472	0.45	0.652
KSS					
1-year	Dose	0.002	0.950	0.00	0.998
	Source	5.72	2.165	2.65	0.008
2-year	Dose	1.321	1.23	1.07	0.286
	Source	5.106	2.24	2.28	0.023
KOOS					
1-year	Dose	2.188	1.166	1.88	0.061
	Source	1.49	1.650	0.90	0.366
2-year	Dose	0.904	1.102	0.82	0.412
	Source	0			

WOMAC=Western Ontario McMaster Universities Osteoarthritis Index; KOOS=Knee osteoarthritis outcome score; KSS=Knee scale score; VAS=Visual Analogue Scale; SE=Standard error

the control group, intra-articular injection of PRP paired with MSCs significantly decreased the VAS score and the KOOS. This was discovered by another systematic review and meta-analysis of nine RCTs.[48] Our meta-analysis of 26 papers including 739 participants revealed that MSCs significantly reduced pain as measured by the WOMAC, VAS, KOOS, and KSS scores. MSCs can be extracted from a variety of tissues, such as adipose tissue, bone marrow, and umbilical cord; nevertheless, our investigation revealed no significant relationship between the MSCs' source and efficacy. According to a meta-analysis and systematic review of RCTs assessing the safety and effectiveness of using scaffolds and MSCs together to treat KOA, the most popular source of MSCs was AD-MSCs.[49] When we looked at the effects of MSC injection in comparison to other techniques such as surgery, corticosteroid medication, and HA injection, we discovered that MSCs not only lessened patients' direct pain but also ensured that they would not experience severe inflammation or complications following joint replacement surgery.

In our study, in the majority of studies, no AEs were reported. The safety of intra-articular injections of MSCs in managing KOA has been evaluated in several RCTs. A systematic review and meta-analysis of six controlled clinical trials found no significant difference in adverse reactions between the MSCs + PRP and the control group.[47]

One of the biggest issues these patients have is pain, which is generally effectively reduced when MSCs are injected

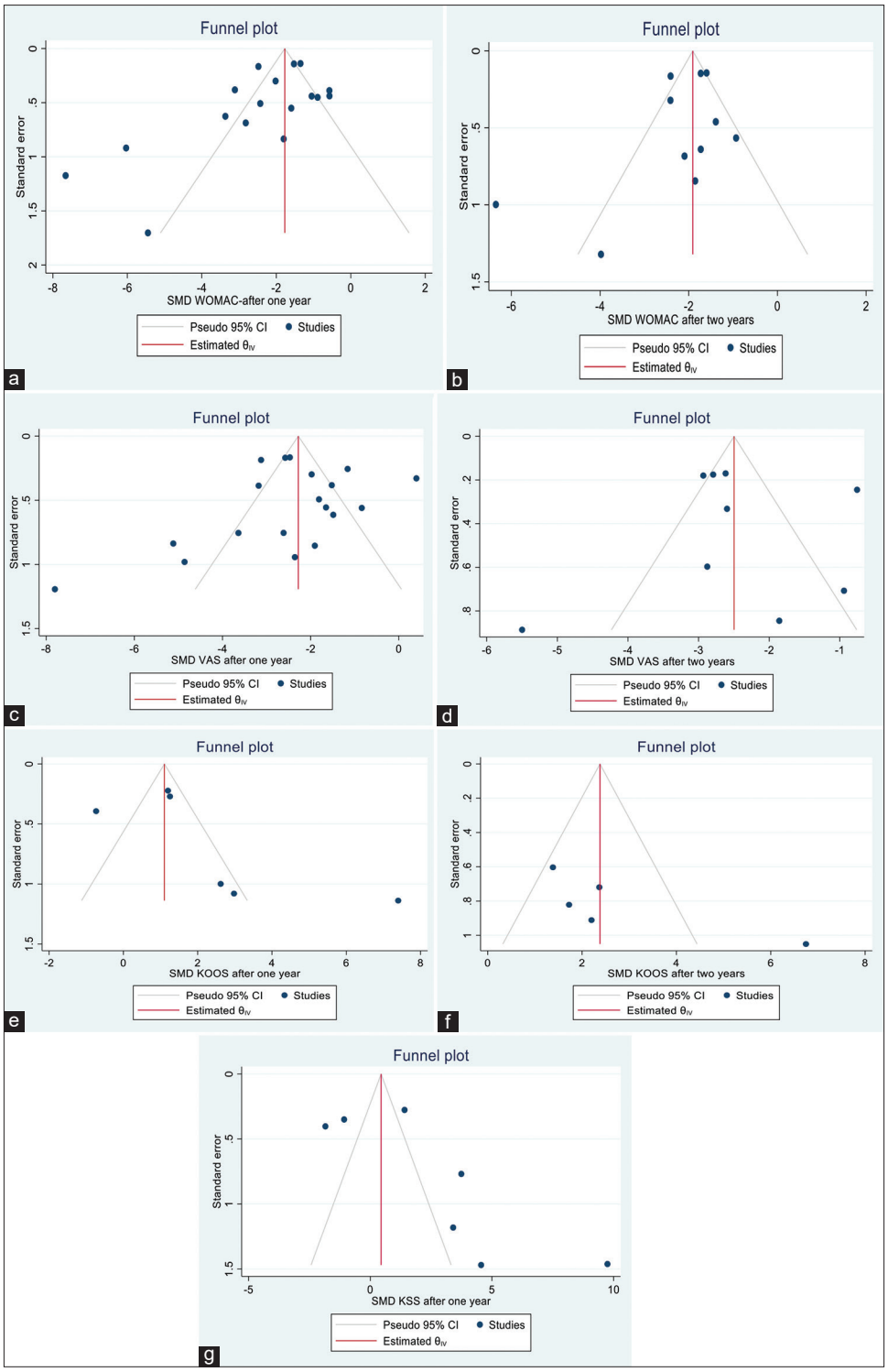

Figure 7: Funnel plot Western Ontario and McMaster Universities Osteoarthritis Index, Visual Analogue Scale, knee osteoarthritis outcome score, and Knee Society Score (KSS) index after 1 and 2 years from follow-up. (a and b) WOMAC's funnel plot after 1 and 2 years. (c and d) VAS's funnel plot after 1 and 2 years. (e and f) KOOS's funnel plot after 1 and 2 years. (g) KSS's funnel plot after 1 and 2 years

into their wounded joints. However, the treatment's proportional risk of side effects is not equal to that of the outdated procedures; therefore, there will not be any serious side effects. The potential of MSCs in the treatment of KOA was highlighted in this study, which offered a thorough examination of the role of regenerative and translational medicine in this regard. With their exceptional capacities for cellular differentiation, their immunomodulatory qualities, and their ability to secrete compounds with biological activity, MSCs are highly attractive as potential treatments for OA of the knee. The evidence demonstrated that MSCS transplantation led to statistically significant improvements

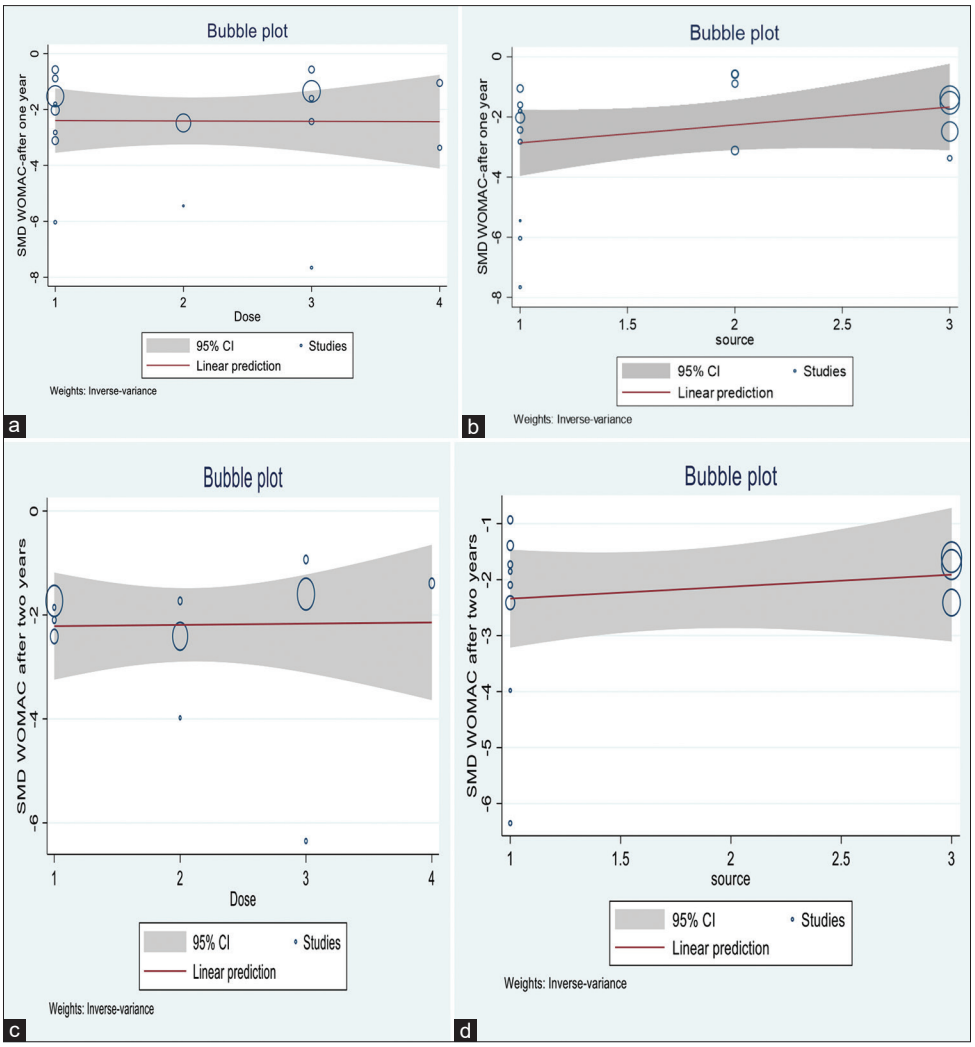

Figure 8: Association standard mean difference (SMD) Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) index with a source of mesenchymal stem cell (MSC) and dose MSC (after 1 and 2 years from follow-up with. (a) Dose with SMD WOMAC after 1 year, (b) Source with SMD WOMAC after 1 year, (c) Dose with SMD WOMAC after 2 years, (d) Source with SMD WOMAC after 2 years

in functional outcomes. These findings underscored the regenerative potential of MSCs in repairing degenerated cartilage at the articular surface, which was a significant factor in alleviating the symptoms of KOA. Furthermore, the analysis established that a moderate dosage of MSCs was sufficient to achieve optimal results, emphasizing the importance of dosage optimization in MSCS therapy. The study also emphasized the necessity of more research projects to improve treatment plans, deal with moral dilemmas, and resolve practical difficulties in the clinical application of stem cell therapies for OA in the knee. One of our limitations was that some of the articles did not have a control group, the number of samples was small, and they did not report randomization in the methodology. Furthermore, some studies only reported some outcomes. Many of the included studies primarily employed subjective functional outcome measures, which inherently carried a risk of bias. Furthermore, the lack of blinding in most studies introduced the potential for treatment bias from both patients and observers. The heterogeneity observed in reported outcomes could be attributed to the variability in treatment protocols employed across the individual studies and the inclusion of patients at different stages of the disease. However, more studies are needed to determine the optimal source of MSCs and this treatment modality's long-term safety and efficacy.

CONCLUSION

Intra-articular injections of MSCs have shown promise in managing OA. Overall, this systematic review and meta-analysis provide comprehensive information about the efficacy and safety of intra-articular injections of MSCs in the management of KOA. It also showed no significant difference between the dose of MSCs and the efficacy of MSCs. This study highlighted the considerable potential of MSCS transplantation as a promising therapeutic modality for KOA within regenerative and translational medicine.

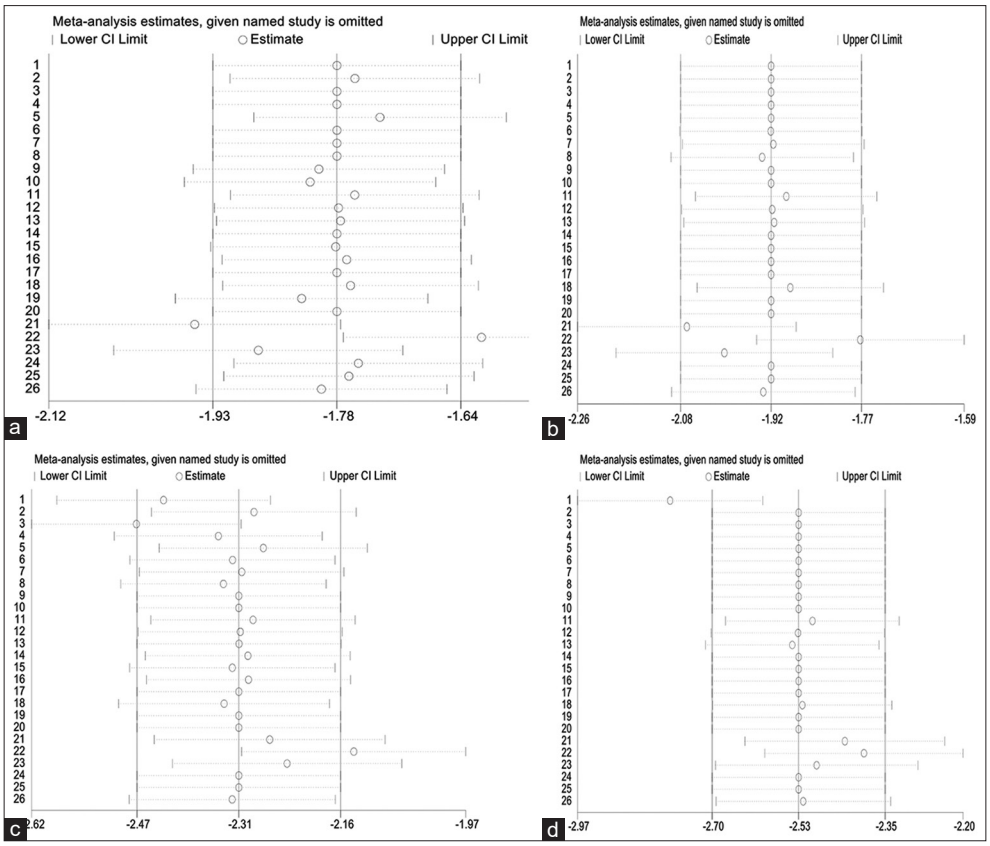

Figure 9: Sensitivity analysis, given named the study omitted. (a) Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) index after 1 year, (b) WOMAC index after 2 years, (c) Visual Analogue Scale (VAS) index after 1 year, (d) VAS index after 2 years

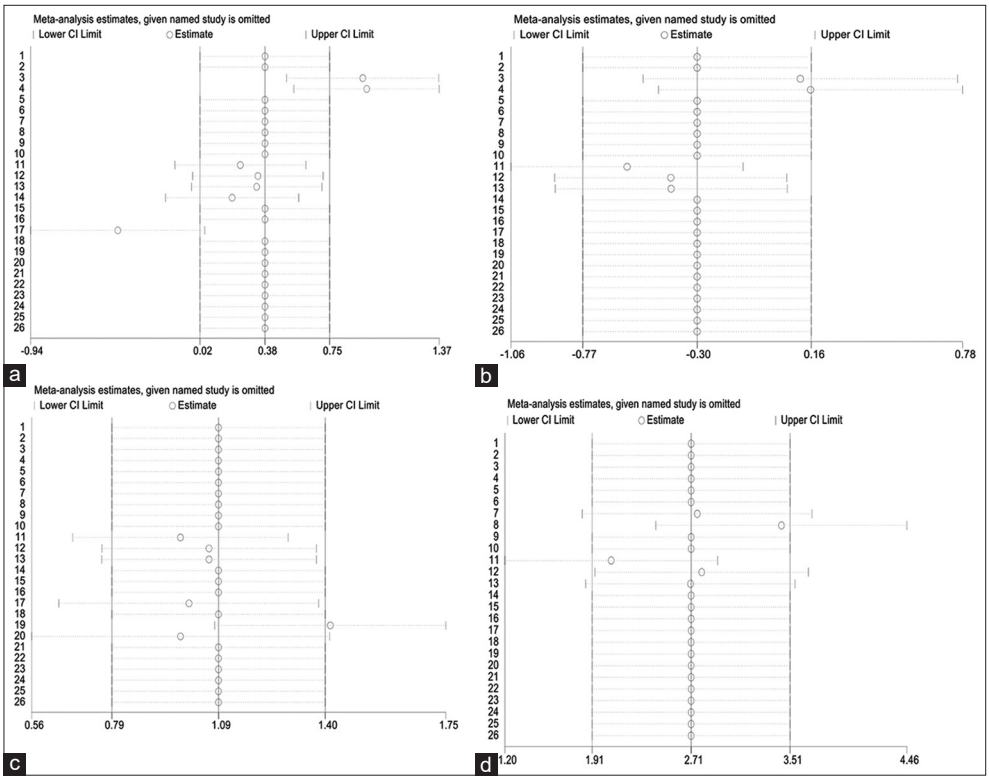

Figure 10: Sensitivity analysis, given named the study omitted. (a) Knee society score (KSS) index after 1 year, (b) KSS index after 2 years, (c) Knee osteoarthritis outcome score (KOOS) index after 1 year, (d) KOOS index after 2 years

However, it underscored the importance of rigorous research, standardization, and ethical considerations to ensure the reliability and applicability of MSCS therapies for KOA.

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Conflicts of interest

There are no conflicts of interest.

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