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REVIEW

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Efficacy and safety of mesenchymal stem cells in knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background The aim of this meta-analysis was to investigate the efficacy and safety of intra-articular injection of mesenchymal stem cells (MSCs) alone for the treatment of unoperated knee osteoarthritis (OA).

Methods Four databases were systematically searched (before August 1, 2024) to include randomized controlled trials (RCTs) of MSCs for OA. The population of this study was OA patients who had not received any surgical treatment. The intervention was intra-articular injection of MSCs without other adjuvant therapy. Outcomes included Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), 100-mm Visual Analog Score (VAS), Knee Injury and Osteoarthritis Prognostic Score (KOOS), and adverse events. After screening the literature according to the eligibility criteria, extracting the data, and evaluating the quality, Meta-analysis was performed using Revman 5.3 software. The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results 8 RCTs and 502 patients with OA were included in the study. Compared with the control group, MSCs significantly improved 6-month WOMAC [MD = 7.44, 95% CI = (1.45, 13.42), $P = 0.01$] and 12-month WOMAC [MD = 10.31, 95% CI = (0.96, 19.67), $P = 0.03$]. MSCs also improved VAS and KOOS at 6 and 12 months in patients with OA. Subgroup analysis showed more significant efficacy of adipose source and high doses of MSCs. There was no significant difference between the adverse events in the MSCs group and the control group ($P > 0.05$).

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Conclusion Intra-articular injection of MSCs alone could significantly improve knee pain and dysfunction in patients with unoperated OA. MSCs are expected to be an effective treatment for OA with enhanced delivery efficiency.

Keywords Mesenchymal stem cells, Knee osteoarthritis, Intra-articular injection, Randomized controlled trial, Meta-analysis

Introduction

Knee osteoarthritis (OA) is a highly and increasingly prevalent degenerative musculoskeletal disorder. The incidence of OA is 203/10,000 per year and affects approximately 650 million people aged 40 years and older worldwide [1]. Further, OA is an important cause of disability and is characterized by morning stiffness, knee pain and swelling, joint deformity, and functional impairment [2]. Current nonoperative treatments include medications (nonsteroidal anti-inflammatory drugs, hyaluronic acid, and corticosteroids) and functional therapies (exercise, education, and weight loss) [3]. Currently, there are no drugs that can reverse the natural progression of OA [4]. At the end stage of OA, most patients require knee replacement surgery as their quality of life is severely affected [5, 6]. As a result of global aging and the increase of obesity, OA places a growing burden on families and society. It is estimated that OA costs more than 300 billion dollars a year in healthcare costs and wages lost [7].

It is well known that OA is a common disease with multiple risk factors, which include obesity, aging, female, a previous knee injury, weak thigh muscles and work that requires long periods of squatting and kneeling [8, 9]. The pathology of OA is characterized by degeneration and destruction of articular cartilage and menisci, inflammation and fibrosis of the infrapatellar fat pad and synovial membrane, and sclerosis of subchondral bone [10–12]. At the early stages of OA, synovial effusion and synovial thickening within the joint could increase inflammation and further advance the progression of OA [13, 14]. Therefore, reducing inflammation might alleviate the deleterious changes of structures in the knee joint and consequently treat OA.

With the development of regenerative medicine, mesenchymal stem cells (MSCs) with multispectral differentiation potential have been used as a potential treatment for liver cirrhosis, diabetic nephropathy, pulmonary fibrosis, sepsis, and COVID-19 [15–19]. MSCs can differentiate into chondrocytes for articular cartilage repair under specific induction [20, 21]. In addition, MSCs could regulate local inflammatory responses and immunity functions by secreting paracrine factors and extracellular vesicles (EVs) [22, 23]. MSCs also modulate the local microenvironment of the knee joint by releasing growth factors/cytokines and mediating intercellular communication [24]. Therefore, MSCs from a wide range of sources (bone marrow-derived, adipose tissue-derived, and umbilical cord-derived) have shown great promise in reducing inflammation, repairing damaged articular cartilage, and slowing down the progression of OA due to their low immunogenicity, immunomodulatory and anti-inflammatory effects, homing effect, good differentiation capacity, and less ethical issues [25–27].

Recently, the isolation and extraction, culture, and preparation methods of MSCs have been gradually standardized and industrialized [28–31]. Furthermore, with the emergence of several high-quality RCTs (randomized controlled trials), it is necessary to summarize clinical evidence to investigate the efficacy and safety of MSCs in OA [32–34]. Some previous meta-analyses have shown that MSCs are effective in relieving pain and improving function in patients with OA [35–39]. However, these studies had some limitations including small sample size, introduction of other therapies, and injections containing other component. The meta-analysis by Song et al. included not only RCTs, but retrospective studies and cohort studies, which would result in lower clinical evidence level [36]. The meta-analysis by Xie et al. and the meta-analysis by Huang et al. included several studies that used mixture of MSCs and other components (platelet-rich plasma or bone marrow concentrate) and several studies that used surgical therapies (microfracture, high tibial osteotomy, arthroscopic debridement) in addition to MSCs, which would interfere with evaluation of MSCs efficacy [37, 38]. Therefore, this study aimed to compare the efficacy and safety of preoperative intra-articular injection of MSCs alone for the treatment of OA to avoid interference of other therapeutic measures in the assessment of the efficacy of MSCs. Moreover, the study only included RCTs with the highest level of evidence to clarify the treatment effect of MSCs. In addition, subgroup analyses were performed to explore whether MSCs from different sources or at different doses had heterogeneity in the treatment of OA.

Methods

This study was conducted according to the Cochrane Handbook for Systematic Reviews and the PRISMA statement guidelines [40, 41]. The PRISMA checklist could be found in Additional file 3. In addition, this study was registered on Prospero and the registration number is CRD42024571190.

Search strategy

Web of Science, PubMed, EMBASE, and Scopus were systematically searched. In this study, we systematically searched for eligible studies from database creation to August 1, 2024, using "mesenchymal stem cells" and "osteoarthritis" and their free words as keywords. The language of this study was limited to English. The detailed search strategy is described in Additional File 1.

Two authors (Cao and Ou) selected studies that might meet the criteria by reviewing titles, abstracts, and keywords. After initial screening, full-text review was performed to exclude studies that did not meet the eligibility criteria. In addition, we searched the references of the included studies. Consultation was conducted to resolve differences. The eligibility criteria for this study met the PICOS principles.

Inclusion criteria: population (P): Patients with a diagnosis of OA, regardless of country, region, or race. Intervention (I): Regional injection of MSC without surgical treatment. Comparison (C): Regular medication or placebo. Outcome(O): Primary outcome: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); secondary outcomes: Visual Analog Score (VAS) for Pain, Knee Injury and Osteoarthritis Outcome Score (KOOS), and adverse events. Study design(S): RCT. Exclusion criteria: patients who have undergone knee arthroplasty or other surgical treatments; studies using treatments such as bone marrow concentrates, PRP, etc.; animal or cellular experiments; reviews or comments, conference abstracts, etc.; prospective cohort studies; systematic evaluations and Meta-analyses.

Data extraction

Data for each RCT were extracted independently by two authors (Cao and Ou) and any unresolved differences were resolved by consensus. The main contents are as follows: (1) Baseline information: title, author's name, country, and time of publication. (2) Study Characteristics: sample size, mean age, cell type and dose, and duration of follow-up. (3) Primary endpoints: WOMAC at 6 and 12 weeks. (4) Secondary endpoints: VAS and KOOS at 6 and 12 weeks and adverse events.

Assessment of risk of bias

The quality and risk of bias of the included RCTs were assessed by using the Cochrane Risk of Bias Assessment Tool [42]. The Cochrane Risk of Bias Assessment Tool includes selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. All areas were assessed as low risk of bias, unclear risk of bias, and high risk of bias. The disagreements were decided by consensus.

Statistical analysis

All meta-analyses were performed through Review Manager (version 5.3, Cochrane Collaboration). For continuous variables, 95% confidence intervals (CI) were used to determine the WMD (weighted mean difference) or SMD (standardized mean difference). For dichotomized variables, OR and 95% CI were used. After standardized chi-square tests were performed, heterogeneity was assessed based on P and I^2 values. If heterogeneity was high, a random effects model was used ($P<0.05$, $I^2>50\%$). When heterogeneity was low, a fixed-effects model was used ($P>0.05$, $I^2<50\%$). A two-sided $P<0.05$ was considered a statistically significant effect. Funnel plots were used to investigate publication bias.

In the process of extracting data, it is sometimes necessary to merge data from various subgroups. If the data is a continuous variable, the following formula is required: Let the sample size of subgroup A be N_1, the mean be M_1 and the standard deviation be SD_1; the sample size of subgroup B be N_2, the mean be M_2 and the standard deviation be SD_2. Then the merged sample size is $N=N_1+N_2$, the merged mean is $M=\frac{N_1M_1+N_2M_2}{N_1+N_2}$, the merged standard deviation is $SD=\sqrt{\frac{(N_1-1)SD_1^2+(N_2-1)SD_2^2+\frac{N_1N_2}{N_1+N_2}(M_1^2+M_2^2-2M_1M_2)}{N_1+N_2-1}}$

If there are multiple subgroups of data to be merged, the data from two subgroups will be merged first according to the above formula, and then the resulting data will be merged with the third subgroup, and so on.

Results

Study selection

A total of 12,229 relevant studies were systematically searched. 6843 duplicate records were excluded. After further screening by title and abstract, 52 studies were considered to potentially meet the eligibility criteria. Finally, a total of 502 patients from 8 RCTs were included in the meta-analysis [32–34, 43–47]. The detailed selection flow is shown in Fig. 1.

Study characteristics

Among all included RCTs, 2 were from China, 2 from South Korea, and 2 from Spain. The time of publication was from 2015 to 2023. For the times of injections, only one study (Freitag 2019) had a one-injection group and a two-injection group [44], while the other seven studies all used a single injection. For dose levels, one study (Lamo-Espinosa 2016) had two different dose levels and one study (Chen 2021) had three different dose levels [34, 47], while the other six studies used a single dose. For cell source, five studies injected adipose-derived mesenchymal stem cells (ADMSCs), and the other three studies injected bone marrow mesenchymal stem cells

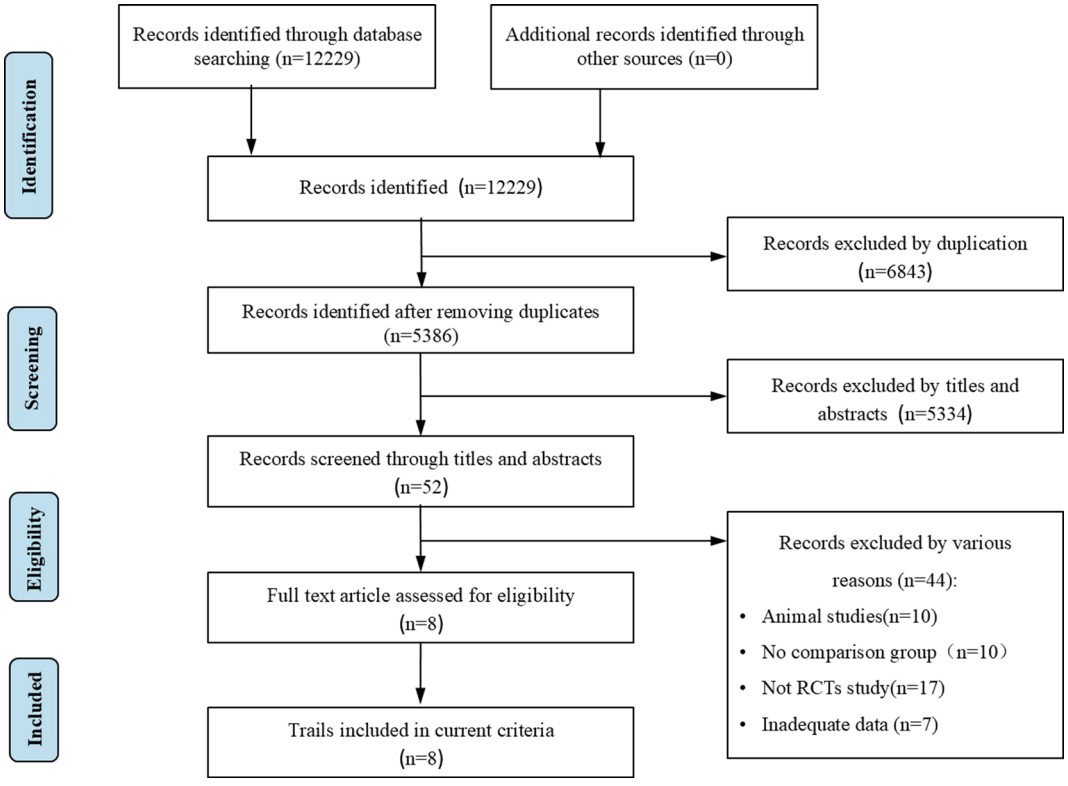

Fig. 1 Preferred reporting items for systematic reviews

(BM-MSCs). The sample sizes of all studies ranged from 24 to 252. Altogether, Table 1 presents the detailed characteristics of the included RCTs.

Risk of bias

The risk of bias for the 8 RCTs was summarized in Fig. 2. The results found that 4 studies mentioned randomized sequence generation (low risk of bias) while 2 studies mentioned allocation concealment (low risk of bias). For blinding of patients, five studies were low risk and one was unblinded (high risk of bias). For blinding of outcome assessment, four studies were low risk and one study was high risk. All RCTs had complete results (low risk of bias) and none had selective reporting bias (low risk of bias). Regarding other biases, all RCTs were at low or unclear risk. No publication bias was detected in the funnel plot (Additional file 2: Figure S3).

Primary outcome

6M-WOMAC

Six studies assessed WOMAC at 6 months after injection. 4 of these studies provided complete subscore data (pain, stiffness, function). For pain subscore, heterogeneity was low ($I^2 = 22\%$, fixed-effects model). Compared with the control group, patients with OA showed a significant improvement in pain subscore after treatment with MSCs [MD = 1.13, 95% CI = (0.45, 1.81), $P = 0.001$] (Fig. 3A). Heterogeneity of stiffness subscore was low ($I^2 = 0\%$, fixed-effects model). There was a significant improvement in the stiffness subscore after treatment with MSCs compared with the control group [MD = 0.49, 95% CI = (0.11, 0.86), $P = 0.01$] (Fig. 3B). The heterogeneity of the functional subscore was low ($I^2 = 43\%$, fixed-effects model). There was a significant improvement in the functional subscore of the WOMAC after treatment with MSCs [MD = 3.36, 95% CI = (0.98, 5.73), $P = 0.006$] (Fig. 3C). For the total WOMAC, heterogeneity was relatively high ($I^2 = 67\%$, random effects model). There was a significant improvement in the total WOMAC after MSCs for OA compared to the control group [MD = 7.44, 95% CI = (1.45, 13.42), $P = 0.01$] (Fig. 3D).

12 M-WOMAC

A total of 5 studies followed up WOMAC at month 12, 3 of which provided complete subscore data (pain, stiffness, function). Heterogeneity of pain subscore was low ($I^2 = 0\%$, fixed-effects model). Pain subscore was significantly improved in patients with OA after MSC treatment [MD = 1.03, 95% CI = (0.02, 2.03), $P = 0.04$] (Fig. 4A). Heterogeneity in stiffness subscore was low (I2 = 0%, fixed-effects model). Compared with the control group, there was a significant improvement in the stiffness subscore in the MSCs group [MD = 0.65, 95% CI = (0.02, 1.27), $P = 0.04$] (Fig. 4B). Heterogeneity in

Table 1 Characteristics of the included trials and participants

Author	Year	Country	Design	Age (exp/con)	Cell type	Cell dose	Source	Follow up	Main Outcome measures	Patient (exp/con)
Kim et al.	2023	Korea	RCT	63.7, 63.8	ADMSCs	1×10^8	Abdominal subcutaneous fat	3, 6 months	WOMAC, VAS, KOOS	125, 127
Chen et al.	2021	China	RCT	67.6, 70.5	ADMSCs	64×10^6, 32×10^6, 16×10^6	Abdominal subcutaneous fat	2, 4, 12, 24, 36, 48 weeks	WOMAC, VAS	49, 8
Bastos et al.	2019	Portugal	RCT	58, 55.9	BM-MSCs	4×10^7	Bone marrow aspirate from both posterior iliac crests	12 months	KOOS, ROM	16, 17
Lu et al.	2019	China	RCT	55, 59.6	ADMSCs	5×10^7	Abdominal subcutaneous fat	6, 12 months	WOMAC, VAS	23, 24
Lee et al.	2019	Korea	RCT	62.2, 63.2	ADMSCs	1×10^8	Abdominal subcutaneous fat	3, 6 months	WOMAC, VAS	12, 12
Freitag et al.	2019	Australia	RCT	54.6, 51.5	ADMSCs	1×10^8 single time or two times,	Abdominal subcutaneous fat	1, 3, 6, 12 months	KOOS, WOMAC	19, 10
Lamo-Espinosa et al.	2016	Spain	RCT	61.9, 60.3	BM-MSCs	1×10^8, 1×10^7	Bone marrow aspirate from both posterior iliac crests	3, 6, 12 months	WOMAC, VAS	20, 10
Vega et al.	2015	Spain	RCT	57, 57	BM-MSCs	4×10^7	Bone marrow aspirate from both posterior iliac crests	12 months	VAS, WOMAC	15, 15

Con: control group; Exp: experimental group; UK: unknown; RCT: randomized controlled trial; ADMSCs: adipose-derived mesenchymal stem cells; BM-MSCs: bone marrow mesenchymal stem cells; VAS: 100-mm visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KOOS: Knee Injury and Osteoarthritis Outcome Score

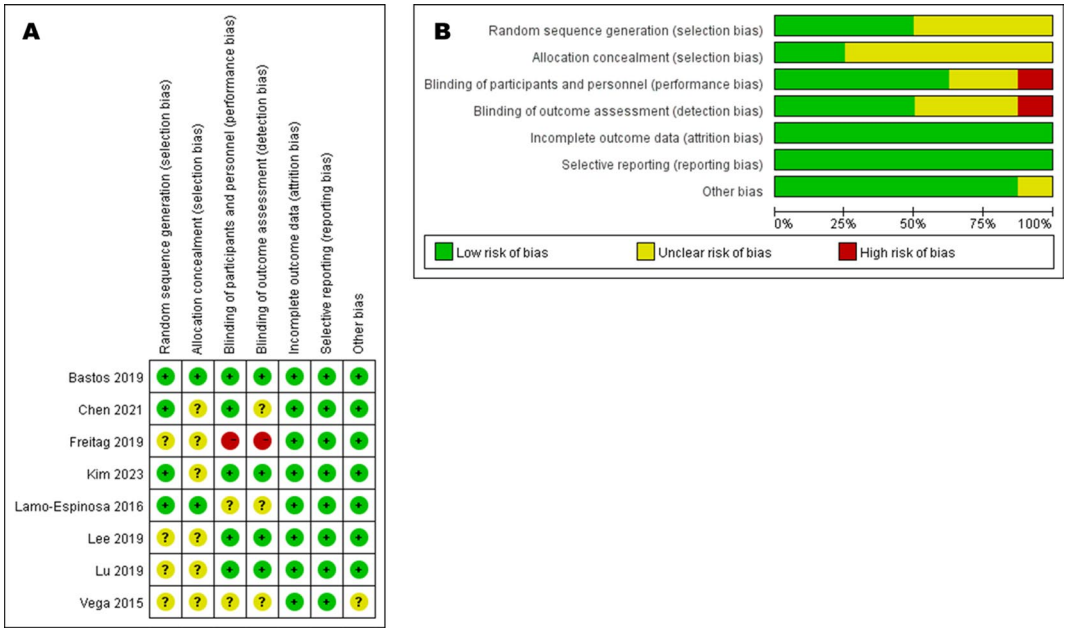

Fig. 2 (**A**) Risk of bias included in the randomized controlled trials. (**B**) Risk of bias graph

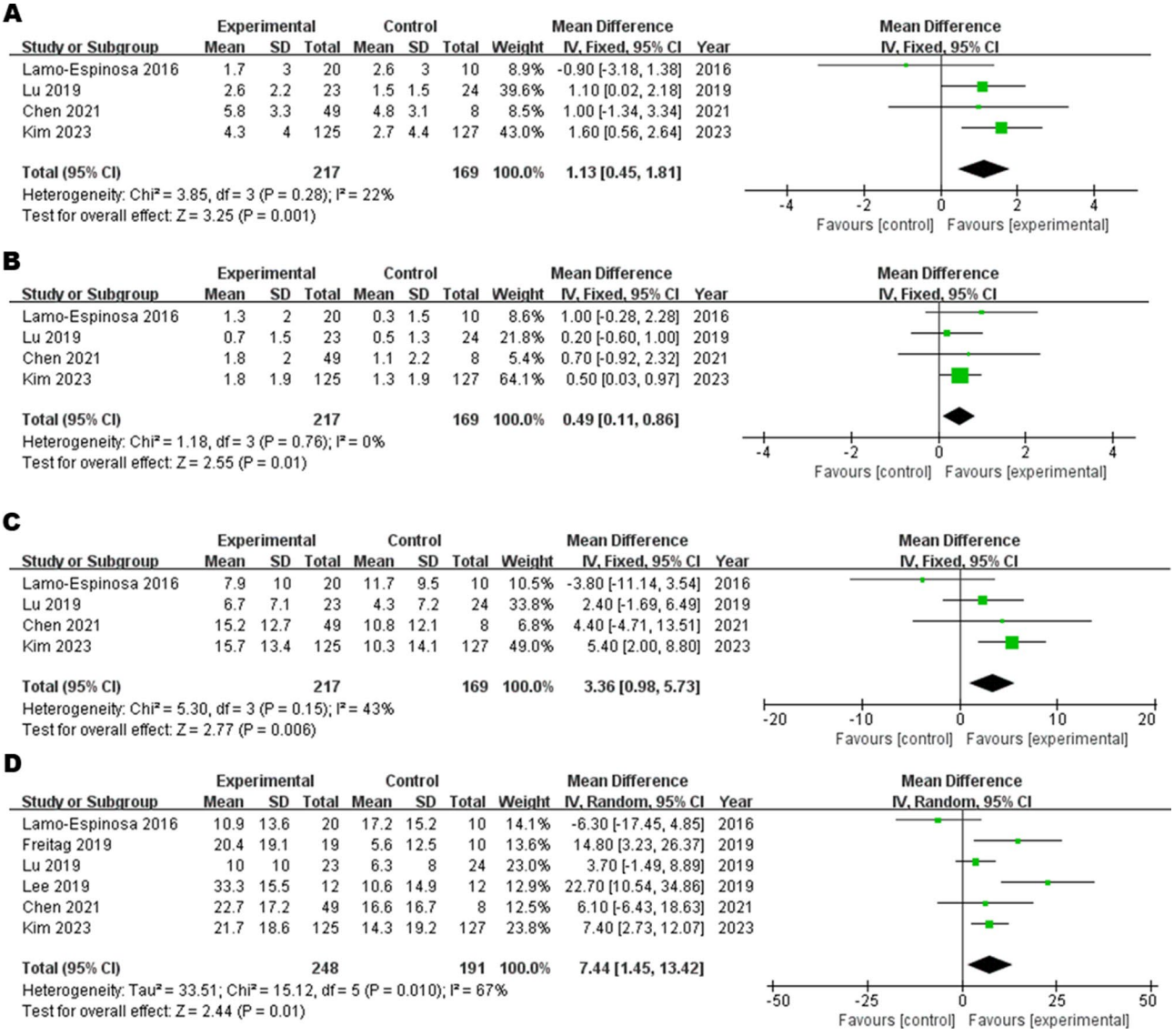

Fig. 3 Forest plot of 6 M-WOMAC, (**A**) pain subscore, (**B**) stiffness subscore, (**C**) function subscore, (**D**) total score

functional subscore was relatively high ($I^2 = 57\%$, random effects model). There was no significant difference between the two groups [MD = 0.82, 95% CI = (-4.33, 5.97), $P = 0.76$] (Fig. 4C). Heterogeneity of total WOMAC was high ($I^2 = 77\%$, random-effects model). Improvement in total WOMAC was significantly higher in the MSCs treatment group than in the control group [MD = 10.31, 95% CI = (0.96, 19.67), $P = 0.03$] (Fig. 4D).

Dose subgroups

All studies were categorized into low dose group ($1.0 \times 10^7 - 6.4 \times 10^7$ cells) and high dose group ($1.0 \times 10^8 - 2.0 \times 10^8$ cells). Subgroup analysis showed significant improvement in 6 M-WOMAC in the high-dose group [MD = 8.14; 95%CI= (4.26,12.02); $P = 0.002$] compared to the control group. However, the low-dose group was not statistically different from the control group [MD = 3.20; 95%CI= (-1.29, 7.68); $P = 0.16$] (Fig. 5A). Subgroup analyses showed significant improvements in 12 M-WOMAC in both high-dose [MD = 14.25; 95%CI= (7.44,21.07); $P < 0.0001$] and low-dose groups [MD = 4.84; 95%CI= (0.45, 9.24); $P = 0.03$] compared to the control group (Fig. 5B).

Cell source subgroups

Subgroup analysis showed that 6 M-WOMAC was significantly improved in the ADMSCs group [MD = 7.53; 95%CI= (4.42,10.63); $P < 0.00001$] compared to the control group, while no significant improvement was observed in the BM-MSCs group [MD=-6.30; 95%CI= (-17.45, 4.85); $P = 0.27$] (Fig. 6A). Subgroup analysis showed significant improvement in 12 M-WOMAC in

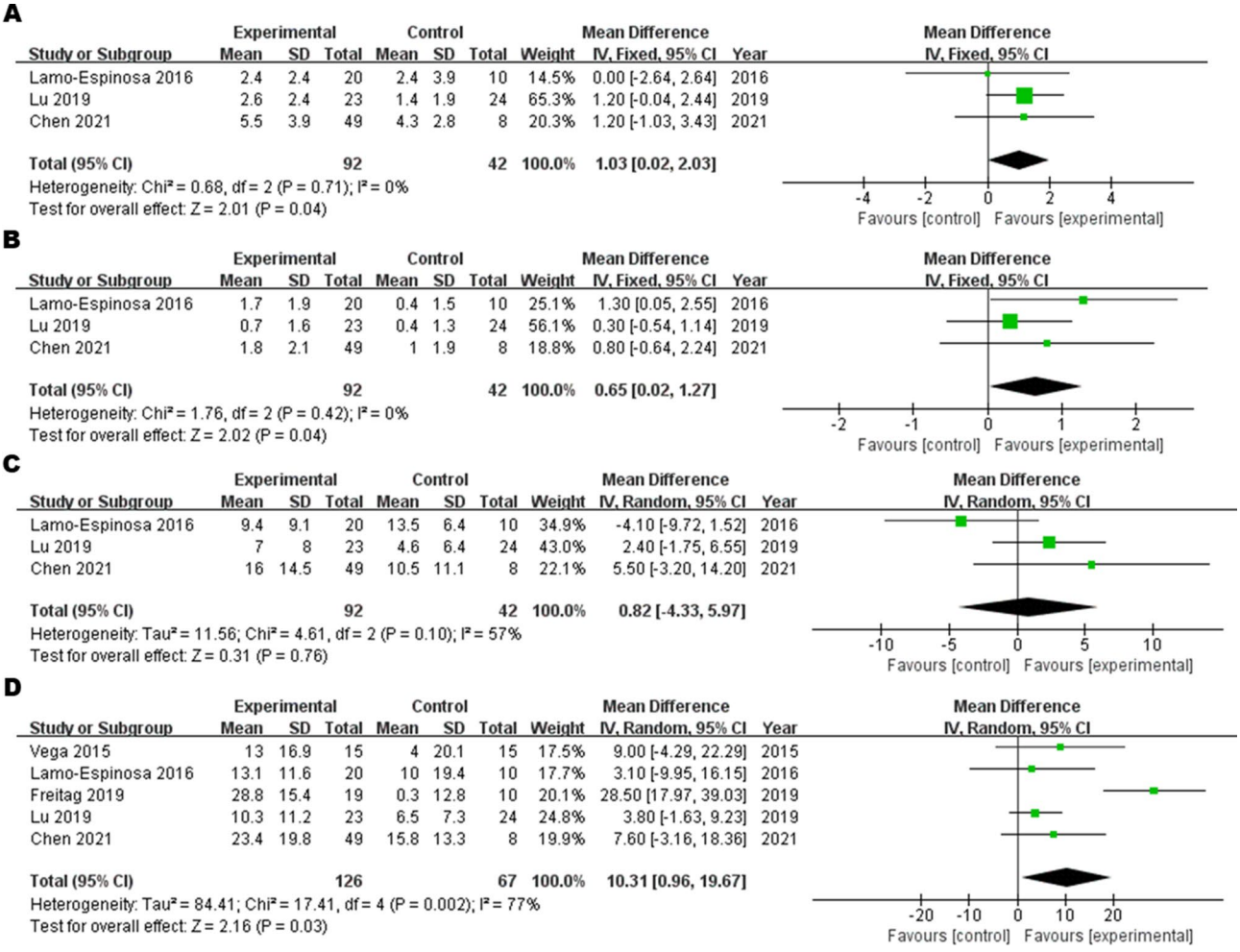

Fig. 4 Forest plot of 12 M-WOMAC, (**A**) pain subscore, (**B**) stiffness subscore, (**C**) function subscore, (**D**) total score

the ADMSCs group [MD = 8.76; 95%CI= (4.35, 13.16); $P < 0.0001$] compared to the control group, whereas there was no significant improvement in the BM-MSCs group [MD = 6.00; 95%CI= (-3.32,15.31); $P = 0.21$] (Fig. 6B).

Secondary outcomes

VAS for pain

Five studies performed a 6-month VAS follow-up while four studies had 12-month VAS follow-up results. The heterogeneity of VAS at 6 months was high ($I^2 = 76\%$, random effects model). Significant improvement in VAS was observed in OA patients treated with MSCs compared to the conventional drugs [MD = 19.39, 95% CI = (8.10, 30.68), $P = 0.0008$] (Fig. 7A). VAS heterogeneity at 12 months was low ($I^2 = 25\%$, fixed effects model). MSCs significantly improved the 12-month VAS in patients with OA [MD = 16.21, 95% CI = (7.38, 25.04), $P = 0.0003$] (Fig. 7B).

KOOS

At the 6th and 12th month follow-up results, symptoms, pain, daily activities, physical recreation, and quality of life were improved in KOOS after MSCs injection compared to the control group (Additional file 2: Figure S1,2).

Safety assessment

We conducted meta-analyses of adverse events (AEs) and serious adverse events (SAEs). The results showed that for AEs [MD = 1.32, 95% CI = (0.85, 2.05), $P = 0.21$] (Fig. 8A) and SAEs [MD = 0.78, 95% CI = (0.23, 2.65), $P = 0.69$] (Fig. 8B), there was no statistically significant difference between the two groups.

Discussion

Compared with conventional treatment, MSC treatment significantly improved WOMAC at 6 (pain, stiffness, and functional subscore) and 12 months (pain and stiffness subscore) in patients with OA. Furthermore, MSC treatment can reduce knee pain (improved VAS for pain) in OA patients without increasing adverse effects.

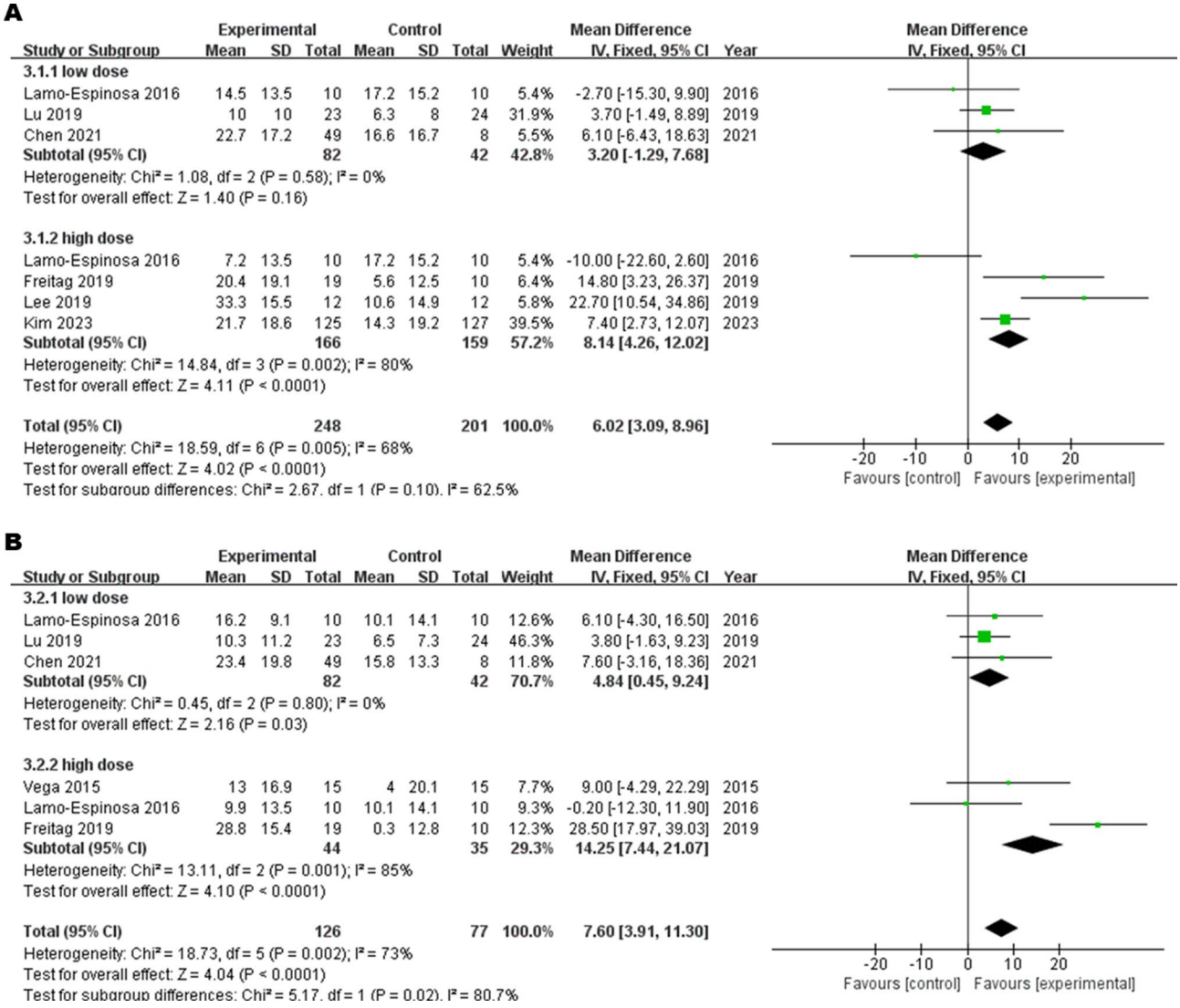

Fig. 5 Forest plot of dose subgroup of (**A**) 6 M-WOMAC total score and (**B**) 12 M-WOMAC total score

Generally, OA affects more than 240 million people worldwide and is a significant cause of years lived with disability [48]. Pain and stiffness caused by OA often limit daily activities of middle-aged and elderly adults and prevent them from living a normal life [49]. In some patients with early OA, relief of pain could be achieved with conservative treatment such as activity modification, physical therapy, nonsteroidal anti-inflammatory drugs, and intraarticular injections of corticosteroid or hyaluronic acid [48, 50]. However, none of these treatments could slow or reverse the progression of OA. What's more, non-steroidal anti-inflammatory drugs and analgesics often have limited effects and significant side effects including gastrointestinal toxicity, bleeding, and decreased renal blood flow with azotemia [48]. Medication could not reverse the progression of the disease due to lack of capability to regenerate cartilage [50, 51]. For those with severe OA, joint replacement is a common treatment but may come with significant surgical risks and rehabilitation cost [49]. Moreover, artificial joints have a limited lifespan (10–15 years) and a high incidence of postoperative complications such as periprosthetic joint infections and loosening or dislocation of prosthesis [52, 53]. Therefore, it is necessary to avoid joint replacement by relieving patients' pain and preserving mobility as far as possible before late-stage OA. During the progression of OA, inhibition of inflammation can reduce damage to the local microenvironment, alleviate pain, and slow down the destruction of the knee joint matrix [4]. As an important therapy in regenerative medicine, MSCs not only stimulate cell proliferation and differentiation but also modulate the immune-inflammatory response [54, 55]. MSCs could affect the functions of most immune effector cells (T cells, B cells, natural

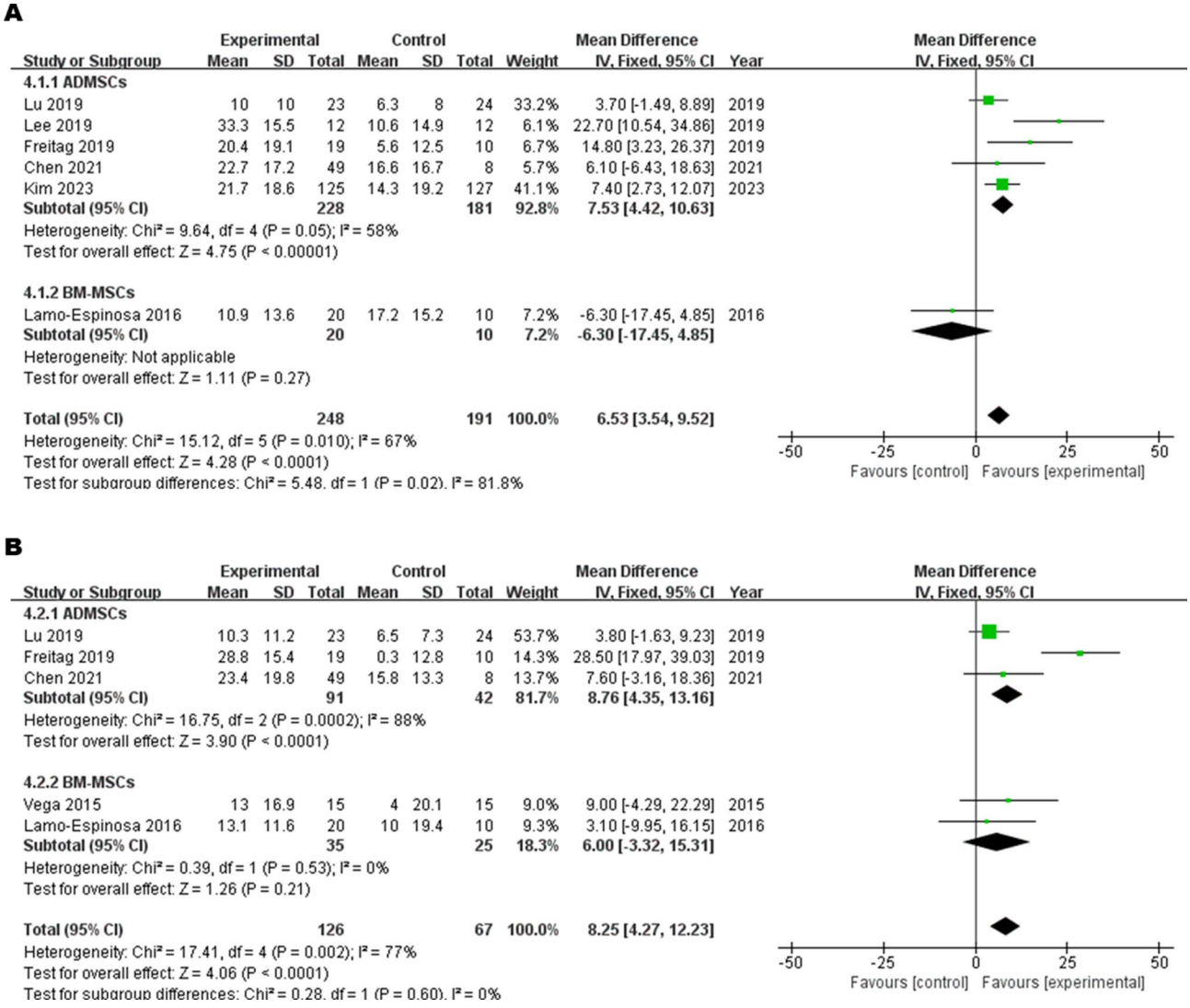

Fig. 6 Forest plot of cell souce subgroup of (**A**) 6 M-WOMAC total score and (**B**)12 M-WOMAC total score

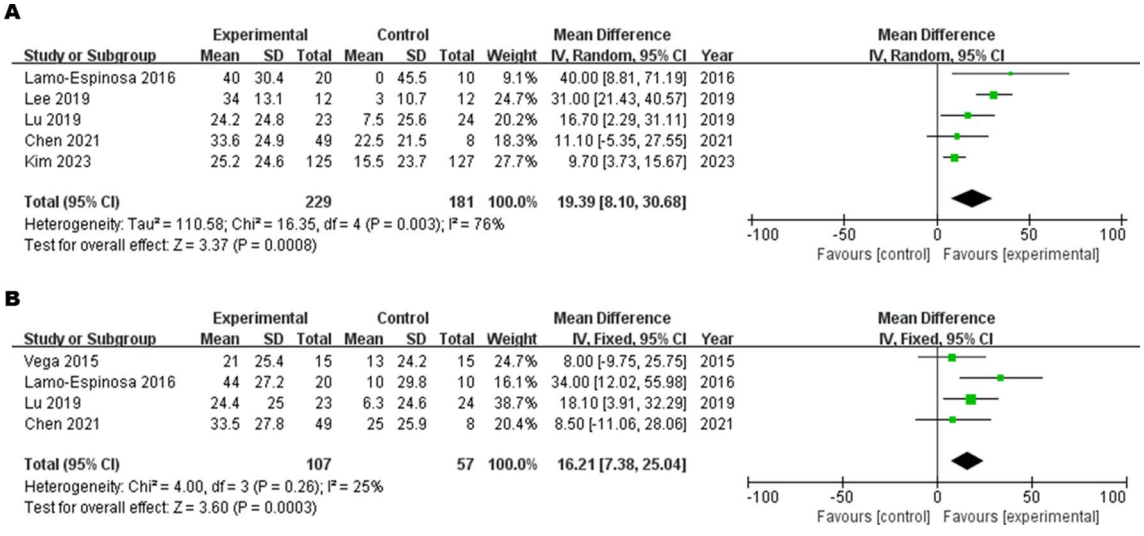

Fig. 7 Forest plot of (**A**) 6 M-VAS score, (**B**) 12 M-VAS score

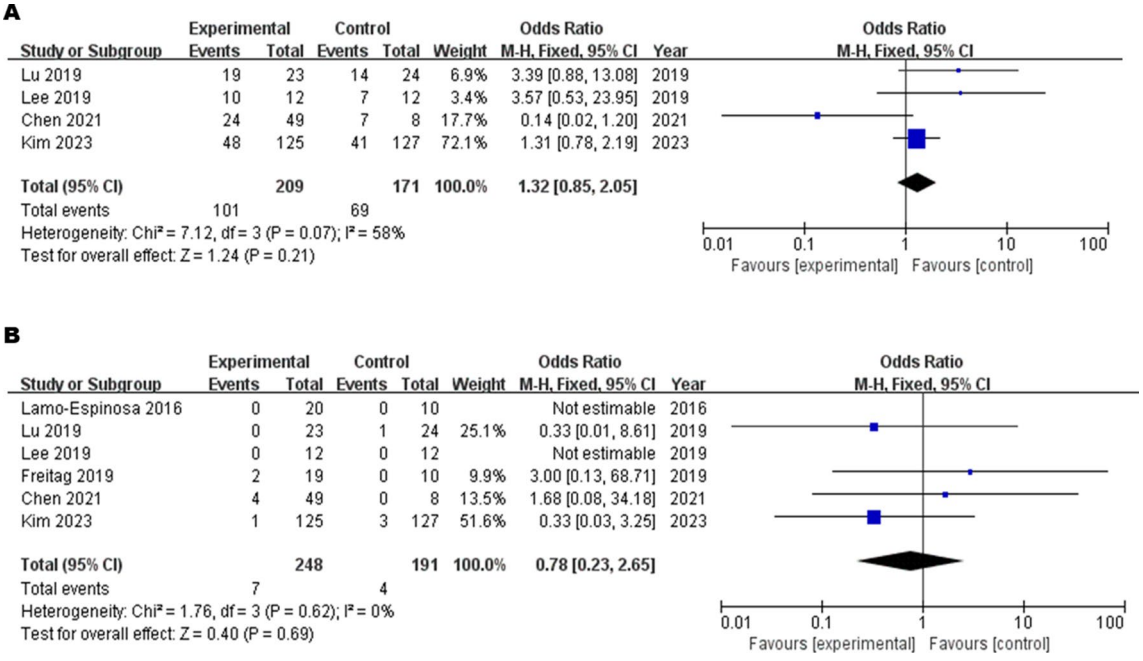

Fig. 8 Forest plot of safety: **(A)** AEs, **(B)** SAEs

killer cells, macrophages, monocytes, dendritic cells, and neutrophils) through cell-to-cell contacts and local microenvironmental factors derived from paracrine activity (exosomes, microvesicles, and apoptotic bodies) [54]. A meta-analysis showed that BMSCs injection could significantly improve cartilage volume [39]. This further suggests that MSCs have important potential in early to mid-stage OA. To investigate the efficacy and safety of MSCs injection alone in the treatment of OA, we excluded studies containing other treatments (PRP, microfracture, arthroscopy) as well as other components (mesenchymal stromal cells, bone marrow concentrate).

For OA, MSCs therapy is now becoming a promising alternative to other non-surgical treatment such as nonsteroidal anti-inflammatory drugs, hyaluronic acid, and corticosteroids [50, 51]. Recently, there was a gradual increase in sample size of clinical trials that injected MSCs. The RCT by Kim et al. in 2023 included 252 patients, which was more than double the number of participants in previous studies [33]. It suggests that MSCs therapy have gained increasing attention from researchers. In terms of patient selection, most studies focused on patients with a mean age of 60 years [32–34, 43–47]. It remains unclear whether OA patients in different age groups share different responsiveness to MSCs treatment, since the risk of developing OA increases with age [1, 51]. The majority of studies on MSCs had a follow-up period of less than one year (3,6,12 month). This may be due to the fact that MSC could not survive in vivo for longer than that time. Future RCTs could perform a longer follow-up to assess the long-term efficacy of MSCs.

For the outcome analysis, we chose WOMAC as the primary outcome indicator and VAS, KOOS, and adverse events as secondary outcomes. WOMAC is widely used in the evaluation of OA and is a self-administered questionnaire consisting of 24 items divided into 3 subscales: pain, stiffness and function. The primary outcomes showed that MSCs significantly improved WOMAC scores at 6 and 12 months in patients with OA. In addition, patients with OA showed significant improvements in pain, stiffness, and function 6 months after injection. The meta-analysis of Xie et al. was similar to our results. However, there may be limitations in the low level of evidence of the included studies and the combined WOMAC follow-up results [37]. Inconsistently, the meta-analysis by Jeyaraman et al. found no significant difference in WOMAC between the BMSCs/AD-MSCs group and the control group. The probable reason for this is that the studies they included were highly heterogeneous and lacked blinding [35]. At 12 months after treatment, pain and stiffness also improved in the MSCs group without significant changes in function. This result suggested that MSCs still have favorable outcomes after one year of treatment. Patients with repaired cartilage may have pain relief and increased knee mobility. The reason for the lack of significant difference in function may be due to repeated abrasion of the repaired cartilage. In general, MSCs could differentiate into chondrocytes and secrete large amounts of cartilage matrix to repair injured cartilage. However, Maheshwer et al. found that MSCs improved cartilage volume but not cartilage quality [39]. After 12 months of treatment with MSCs,

regenerated cartilage may be re-destroyed by repeated abrasion in the long term. It may explain the lack of significant improvement in function. Moreover, some other factors including OA severity, lesion size, and comorbidities might influence patients' self-reported pain and physical function [39].

To reduce heterogeneity between studies, further subgroup analyses of dose and cell source were performed. In the 8 included studies, 5 studies injected ADMSCs, which were all obtained from abdominal subcutaneous fat, while the other 3 studies injected BM-MSCs, which were obtained percutaneously from both posterior iliac crests. Although the MSCs from bone marrow and subcutaneous fat have long been suggested for vanguard therapies in OA, infrapatellar fat pad (IPFP) tissue is also an important source for MSCs [56, 57]. IPFP stem cells are considered to have strong proliferation capability and differentiation potential and have become an attractive cell source for cartilage regeneration [57, 58]. The advantages of IPFP stem cells include being derived from discarded tissue and not requiring a second surgical site. However, the ultrastructural, immunophenotypic, and functional characteristics of the OA-IPFP stem cells could be affected because of inflammatory OA environment (an increase in oxidative stress mediators and accumulation of unfolded proteins) [57, 58]. Hence, the chondrogenic differentiation potential of IPFP stem cells might be reduced. The use of IPFP stem cells in OA is controversial. Besides, It has been shown that synovial-derived MSCs have the greatest chondrogenic potential but are not widely available [59]. In a meta-analysis focusing on the source of MSCs, 12 M-WOMAC was significantly improved and better in the ADMSCs group than in the BMSCs group [35]. Moreover, in terms of source material as well as operating difficulty, ADMSCs may be superior to BMSCs. Operators could easily extract patients' autologous MSCs from their own subcutaneous fat tissue through liposuction. Taken together, the number of MSCs obtained from abdominal subcutaneous fat is significantly greater than those from bone marrow, especially in the elderly population [60]. There is a growing interest in ADMSCs in recent studies [33, 34, 58]. A meta-analysis by Song et al. found better efficacy in MSCs from abdominal subcutaneous fat and foetus [36]. Their study also found significant improvement regardless of MSC dose. In contrast, our results showed that the ADMSCs group and the high-dose group significantly improved 6-month WOMAC, whereas the BMSCs group and the low-dose group provided no significant benefit. Concerning cell dosage, high doses provided better efficacy in the early stages of OA but increased pain and swelling at the injection site. In a meta-analysis exploring the optimal dose of ADMSCs, the high-dose group (1×10^8 cells) may have a greater therapeutic effect on OA compared to the low-dose group (1×10^7 cells) [38], which was similar to our results. It was reported that high doses of MSCs might potentially lead to their expression as M1-type cells with pro-inflammatory responses. Not only that, high cell concentration in the stenotic knee joint could result in cell death [61]. Therefore, future clinical translation should focus on targeted delivery and precise modulation of MSCs. In recent years, umbilical cord-derived mesenchymal stem cells (UC-MSCs) have been used in various tissues due to their low immunogenicity, high proliferation efficiency, high differentiation capacity, wide source, easy mass production, no ethical issues, and immunomodulatory effect [62–64]. In the future, UC-MSCs may be a promising product for the treatment of OA [62, 63, 65–67]. Presently, tissue engineering and nanotechnology have been used to improve the efficiency of stem cell therapy [68, 69]. Another frontier technology, microrobots, could also greatly improve the efficiency of stem cell delivery in the musculoskeletal system [70]. With the aid of these engineering techniques, the future treatment of MSCs is expected to be increasingly safe, efficient, and intelligent.

In the follow-up results at months 6 and 12, there was a significant improvement in VAS and KOOS (Symptoms, Pain, ADL, Sport, QoL) in the MSCs group. Knee pain is the most predominant symptom of OA and is difficult to manage. Shanahan et al. used knee nerve block to relieve short-term pain in patients with OA [49]. Several meta-analyses have shown that MSCs can improve VAS in OA patients [35–38]. In general, MSCs secrete a variety of anti-inflammatory cytokines including IL-10, TGF-β, and IL-1Ra to inhibit inflammation and alleviate the symptoms of OA. MSCs can also regulate overexpressed inflammatory mediators to avoid oxidative damage and apoptosis in normal tissues [71]. A study showed that exogenous MSCs provide lubrication at the synovium of the knee joint apart from synthesizing the cartilage matrix [72]. MSCs may relieve joint pain by lubricating and reducing joint adhesions. In terms of safety, the results showed that there were fewer SAEs in the MSCs group and most of the AEs were self-resolving. Most of the AEs were pain and swelling after injection. Future intra-articular injections of MSCs could be performed under ultrasound guidance to improve the safety of treatment with MSCs [49].

This study also has some limitations. (1) the results of OA were self-reported and subjective; (2) many RCTs did not report AEs and their specific details; (3) there were variations in the inclusion/exclusion criteria of the included studies, which may affect the synthesis of the results; (4) publication bias is an inherent flaw in all meta-analyses.

Conclusion

Meta-analysis of RCTs showed that intra-articular injection of MSCs alone was safe and significantly improved knee pain, function, and quality of life in non-operated OA patients. Subgroup analyses suggested the use of adipose-derived or high-dose MSCs. More large-sample, multicenter RCTs are needed in the future to explore the optimal cell source and dose of MSCs.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Data availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethical approval and consent to participate
No patients were involved in this study.

Consent for publication
Not applicable.

Research registration unique identifying number (UIN)
This study has been registered at Prospero. Registration ID: CRD42024571190.

Competing interests
The authors declare that they have no competing interests.

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