Efficacy of mesenchymal stem cells in treating patients with osteoarthritis of the knee: A meta-analysis

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Abstract. To assess the clinical efficacy and safety of mesenchymal stem cell (MSC) treatment for osteoarthritis of the knee (KOA), a systematic electronic literature search was performed on PubMed, EMBASE and Web of Science. Studies published in English from the earliest record to December 2014 were searched using the following keywords: Cartilage defect, cartilage repair, osteoarthritis, KOA, stem cells, MSCs, bone marrow concentrate (BMC), adipose-derived mesenchymal stem cells, synovial-derived mesenchymal stem cells and peripheral blood-derived mesenchymal stem cells. The effect sizes of selected studies were determined by extracting pain scores from the visual analog scale and functional changes from International Knee Documentation Committee and Lysholm and Western Ontario and McMaster Universities Osteoarthritis Index before and after MSCs or reference treatments at 3, 6, 12, and 24 months. The factors were analyzed and the outcomes were modified after comparing the MSC group pooled values with the pretreatment baseline or between different treatment arms. A systematic search identified 18 clinical trials on this topic, including 10 single-arm prospective studies, four quasi-experimental studies and four randomized controlled trials that used BMCs to treat 565 patients with KOA in total. MSC treatment in patients with KOA showed continual efficacy for 24 months compared with their pretreatment condition. Effectiveness of MSCs was improved at 12 and 24 months post-treatment, compared with at 3 and 6 months. No dose-responsive association in the MSCs numbers was demonstrated. However, patients with arthroscopic debridement, activation agent or lower degrees of Kellgren-Lawrence grade achieved improved outcomes. MSC application ameliorated the overall outcomes of patients with KOA, including pain relief and functional improvement from basal evaluations, particularly at 12 and 24 months after follow-up.

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Introduction

Osteoarthritis (OA) is a chronic, progressive and degenerative joint disease, involving single or multiple joints. OA of the knee (KOA) is the most common disabling disease, characterized by the degeneration and degradation of cartilage, subchondral bone remodeling, osteophyte formation and synovial inflammation, which affects the patient's quality of life and constitutes a heavy financial burden (1-3). With the exception of oral and intra-article injection medications that relieve the symptoms and improve joint function, there is no approved medical treatment that halts disease progression and joint destruction (1,4).

Various surgical methods, including microfracture (5,6) and subchondral drilling (7), have been proposed to regenerate articular cartilage. However, due to the complications and inferior quality of the regenerative fibrocartilage, risky and cost-effective joint replacement surgery is often ultimately required (8). Previous studies have investigated tissue engineering and cellular therapies for treating early stage OA, and autologous chondrocyte implantation has demonstrated positive clinical outcomes (9,10). Nevertheless, due to the poor self-renewal and regeneration potential of chondrocytes, it is a slow process that may lead to fibrocartilage rather than hyaline cartilage (11,12). Furthermore, this two-stage surgical procedure and is predominantly used to treat cartilage defects caused by injury rather than OA.

Therefore, research attention in this field has shifted to the more promising treatment of mesenchymal stem cells (MSCs). MSCs, which can be derived from blood, bone marrow, skeletal muscle, adipose, skin and synovial membrane (13), have the capacity to differentiate into osteocytes, adipocytes, chondrocytes, myoblasts, tenocytes (14,15), secrete bioactive molecules that stimulate angiogenesis and tissue repair, and reduce the response of T cells and inflammation (16,17). Previous clinical trials have reported that mild/moderate OA or advanced OA can be treated efficiently using autologous or allogenic MSCs through implantation, micro fracture or intra-articular injections (18-20). However, so far, no meta-analytic research has evaluated the efficacy and safety of MSCs in treating patients with KOA.

Therefore, the present meta-analysis was conducted to analyze the clinical outcomes of MSC treatment on patients with KOA patients by analyzing pain and functional changes, compared with their pretreatment condition, or placebo controls.

Materials and methods

Search strategy and eligibility criteria. Electronic databases: including PubMed (ncbi.nlm.nih.gov/pubmed), EMBASE (embase.com) and Web of Science (webofknowledge.com), were used to comprehensively search for all relevant studies published in English from the earliest record to December 2014. The following keywords were used: 'cartilage defect', 'cartilage repair', 'osteoarthritis', 'knee osteoarthritis', 'stem cells', 'mesenchymal stem cells' (MSCs), 'bone marrow concentrate', 'adipose-derived mesenchymal stem cells' (ADMSCs), 'synovial-derived mesenchymal stem cells' and 'peripheral blood-derived mesenchymal stem cells', as medical subject headings or text words. In addition, Cochrane Systematic Reviews (cochrane.org/evidence) and ClinicalTrials.gov were manually searched for additional references. Articles were considered eligible if they met the following criteria: i) Patients were ≥18 years-old and had KOA symptom or diagnosed with KOA by clinical and imaging examination; ii) MSCs administered to at least one treatment group; iii) ≥3-month follow-up; iv) ≥1 valid outcome measurement before and after the administration of MSCs, such as the visual analogue scale (VAS), International Knee Documentation Committee (IKDC) Subjective Knee Form, Lysholm scale, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); and v) outcomes were presented as continuous data [mean ± standard deviation (SD)]. Studies that lacked an intervention plan or pain and functional measurements were excluded.

Data extraction and study quality assessment. Two independent reviewers searched the electronic databases and evaluated the eligibility of the searched articles and subsequently extracted data using a standardized form, including data on the study type, number of patients enrolled, patient characteristics, disease duration, dosage of MSCs, outcome measurements, follow-up time and adverse events. If additional data was necessary, the authors were contacted for further information. The Jadad scoring system was used to assess the methodological quality of the randomized controlled trials (RCTs) (21). The quality of the included RCTs ranged from 0-5 points, with a score of <3 indicating a low-quality study. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of other studies according to selection, comparability, exposure, and outcome, including single-arm prospective and quasi-experimental studies (22). NOS was scored out of 9 points, with total scores <4 points defined as low quality. Discrepancies between the two independent evaluations of potential articles were resolved by discussion and consensus.

Data synthesis and analysis. Data were extracted from four time points at or closest to the 3rd, 6th, 12th and 24th months after MSCs treatment. Effect size (ES) was calculated from knee joint pain and functional changes and the results were compared with the pretreatment baseline or between different treatment arms. VAS was extracted from the included articles. If >1 functional measurement was included in an article, only one functional scale in line with the order of IKDC, Lysholm and WOMAC was chosen. As multiple treatment groups wew included in some articles, each group was selected as a separate status set to analysis. Mean ± SD between the pretreatment baseline condition and functional scores after treatment was used to evaluate the effectiveness of MSCs therapy. Positive ES values demonstrated a pain or functional improvement, and vice versa. For studies in which the measurement score and SD was deficient, the value was calculated from the P-value of the corresponding hypothesis test. If the measurement scores and SD could not be extracted in some articles, a correlation of 0.5 was used to estimate the dispersion. A random effect model was used to pool the ESs with a 95% confidence interval (95%CI) on the basis of heterogeneity. A positive pooled ES with a 95%CI >0 indicated an advantage of MSCs compared with the pretreatment condition or reference treatments.

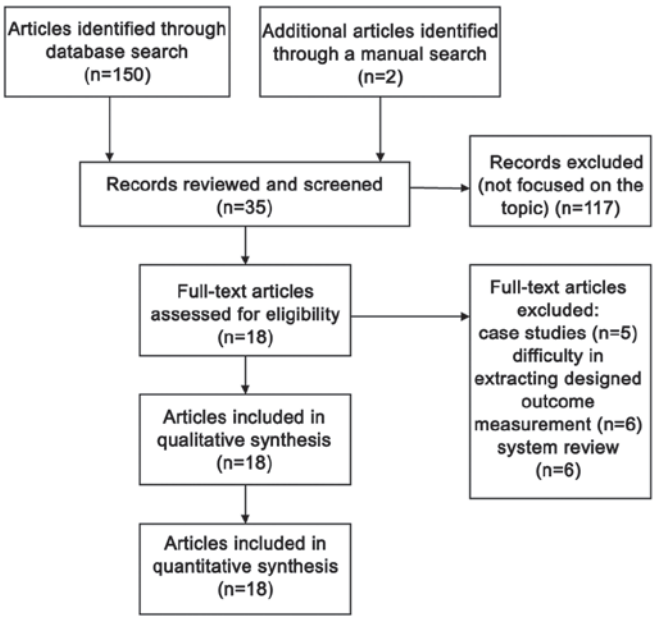


Figure 1. Flow chart of the evaluation process for the inclusion or exclusion of studies.

Assessment of heterogeneity and sensitivity. Statistical heterogeneity was assessed via the I-square and Cochran's Q tests. A P-value of <0.10 for χ^2 test or an I-square >50% was indicative of the existence of substantial heterogeneity (21). Subgroup analysis was performed according to variables of the study design, different dosages, arthroscopic debridement (AD), activation agent, as well as the severity of Kellgren-Lawrence (K-L) grades. Sensitivity analysis was performed by excluding some articles with extreme ES values to assess whether the movement resulted in serious changes in the total result. Funnel plots were used to assess the potential publication bias. All analyses were conducted using Review Manager Version 5.2 (The Cochrane Collaboration, Oxford, UK).

Table I. Summary of studies using MSCs to treat KOA patients.

Author, year	Number of patients	Mean age (year)	BMI	Disease duration	Double blind	ITT	Outcome measure	Follow-up time (month)	Adverse events	Quality assessment	Ref.
Single-arm, prospective follow-up studies											
Buda *et al*, 2010	20 (12M, 8F)	NM	NM	≥12 months	No	Yes	IKDC	6, 12, 24	None	4[a]	(39)
Gobbi *et al*, 2011	15 (10M, 5F)	48 (32-58)	24.5±2.53	NM	No	Yes	VAS, IKDC	6, 12, 24	None	4[a]	(40)
Davatchi *et al*, 2011	4 (2M, 2F)	57.7±5.0	30.25±4.86	≥7 years	No	Yes	VAS	6	None	4[a]	(18)
Emadedin *et al*, 2012	6 (6F)	53.8±8.9	31.6±4.2	NM	No	Yes	VAS, WOMAC	2, 6, 12	None	4[a]	(19)
Koh *et al*, 2013	18 (6M, 12F)	54.6±7.8	NM	≥6 months	No	No	VAS, Lysholm	24	Marked pain in 1 patient	4[a]	(20)
Turajane *et al*, 2013	5 (1M, 4F)	57.2±1.92	25.36±4.46	≥3 months	No	Yes	VAS, WOMAC	1,6	None	4[a]	(41)
Orozco *et al*, 2013	12 (6M, 6F)	49±17.3	NM	≥6 months	No	Yes	VAS, WOMAC	3, 6, 12, 24	Local pain with discomfort in 6 patients	4[a]	(42)
Kim *et al*, 2014	41 (17M, 24F)	60.7 (53-80)	<30	≥12 months	No	Yes	VAS, IKDC	3, 6, 12	Joint swelling in 69 knees, pain in 31 knees	4[a]	(43)
Koh *et al*, 2013	30 (5M, 25F)	70.3 (65-80)	NM	≥12 months	No	Yes	VAS, Lysholm	3, 12, 24	Slight pain in 3 patients	4[a]	(44)
Gobbi *et al*, 2014	25 (16M, 5F)	46.5±8.55	24.4±3.0	≥3 years	No	Yes	VAS, IKDC	12, 24	None	4[*]	(45)
Quasi-experimental studies											
Koh and Choi, 2012	50 (MSCs + PRP group: 8M, 17F; PRP group: 8M; 17F)	MSC group: 54.2±9.3; placebo group: 54.4±11.3	NM	≥12 months	No	Yes	VAS, Lysholm	3, 12	Marked pain with swelling in 1 patient	5[a]	(46)
Koh *et al*, 2014	56 (Group 1: 8M, 13F; Group 2: 14M, 21F)	Group 1: 55.3±4.1; Group 2: 57.4±5.7	Group 1: 26.7±3.1; Group 2: 26.3±3.0	≥12 months	No	No	IKDS	12, 24	None	5[a]	(47)
Jo *et al*, 2014	18 (LDG: 1M, 2F; MDG: 0M, 3F; HDG: 2M, 10F)	LDG: 63±8.6 MDG: 65±6.6 HDG: 61±6.2	LDG: 26±1.0 MDG: 28±2.1 HDG: 26±2.1	≥4 months	No	Yes	VAS, WOMAC	3, 6	Mild (LDG:3; MDG: 2; HDG:5)	5[a]	(48)

Table I. Continued.

Author, year	Number of patients	Average age (year)	BMI	Disease duration	Double blind	ITT	Outcome measure	Follow-up time (month)	Adverse event	Quality assessment	Ref.
Kim *et al*, 2014	54 (MSCs group: 14M, 23F; MSC + fibrin glue group: 8M, 9F)	MSCs group: 57.5±5.9; MSC + fibrin glue group: 57.7±5.8	MSCs group: 26.3±3.2; MSC + fibrin glue group: 27.3±2.9	≥18 months	No	No	IKDC	12, 24	None	5[a]	(49)
Randomized controlled trials											
Varma *et al*, 2010	50 (AD: 25; AD + MSC: 25)	AD group: 48.20±5.13; AD + MSC: 50.67±5.38	NM	NM	No	Yes	VAS	3, 6	None	3[b]	(50)
Saw *et al*, 2013	50 (HAG: 7M, 17F; HA + PBSC group 10M, 15F)	HAG: 42±5.91 HA + PBSC: 38±7.33	HA: 24.83±4.04 HA + PBSC: 24.91±4.15	≥12 months	No	No	IKDS	6, 12, 24	None	3[b]	(51)
Wong *et al*, 2013	56 (HTO + MSC: 15M, 13F HTO: 14M, 14F)	HTO + MSC: 53 (36-54) HTO: 49 (24-54)	HTO + MSC: 23.81±2.17 HTO: 23.89±3.20	NM	No	Yes	IKDS, Tegner, Lysholm	6, 12, 24	None	3[b]	(52)
Vangsness *et al*, 2014	55 (LDG: 11M, 7F; HDG: 14M, 4F HAG: 13M, 6F)	LDG: 44.6±9.82 HDG: 45.6±12.42 HAG: 47.8±8	LDG: 29.86±7.94; HDG: 29.09±5.91; HAG: 26.89± 4.05	NM	Yes	No	VAS, Lysholm	6, 12, 24	Mild (LDG:18; HDG: 17; HAG: 17)	5[b]	(53)

MSC, mesenchymal stem cell; M, male; F, female; BMI, body mass index; ITT, intention-to-treat; HAG, hyaluronic acid group; PBSCs, peripheral blood stem cells; HTO, high tibial osteotomy; VAS, the visual analog scale; IKDC, International Knee Documentation Committee; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. [a]Quality scores derived from the Newcastle-Ottawa scale, [b]quality scores derived from the Jadad scale; NM, not mentioned; LDG, low-dose group; MDG, mid-dose group; HDG, high-dose group; AD, arthroscopic debridement.

Table II. Summary of the preparations and injection details of MSCs in the retrieved trials.

Author, year	MSC origin	Number of cells	Delivery system	Method of implementation	Activation agent	K-L grade	Comparison	Ref.
Single-arm, prospective follow-up studies								
Buda *et al*, 2010	Autologous BMAC	NM	AD	Implantation	HA, membrane scaffold	NM	None	(39)
Gobbi *et al*, 2011	Autologous BMAC	NM	Mini-arthrotomy	Implantation	Collagen matrix	NM	None	(40)
Davatchi *et al*, 2011	Autologous BMSCs	8-9x10^6	None	Intra-articular injection	None	3-4	None	(18)
Emadedin *et al*, 2012	Autologous BMSCs	2.0-2.4x10^7	None	Intra-articular injection	None	4	None	(19)
Koh *et al*, 2013	Autologous AMSCs	1.18x10^6	AD, synovectomy	Intra-articular injection	PRP	3-4	None	(20)
Turajane *et al*, 2013	Autologous BSC	NM	Microfracture	Intra-articular injection	GFAP, HA	2	None	(41)
Orozco *et al*, 2013	Autologous BMSCs	40x10^6	None	Intra-articular injection	None	2-4	None	(42)
Kim *et al*, 2014	Autologous BMSCs	2.4x10^5	Microfracture and AD	Intra-articular injection	Adipose tissues	1-4	None	(43)
Koh *et al*, 2013	Autologous AMSCs	4.04x10^6	Arthroscopic lavage	Intra-articular injection	None	2-4	None	(44)
Gobbi *et al*, 2014	Autologous BMAC	NM	AD	Implantation	Collagen cell sheets	NM	None	(45)
Quasi-experimental studies								
Koh and Choi, 2012	Autologous AMSCs	1.89x10^6	AD, synovectomy	Intra-articular injection	PRP	3	MSCs + PRP vs. PRP	(46)
Koh *et al*, 2014	Autologous AMSCs	3.8x10^6	AD	Implantation	None	1-2	None	(47)
Jo *et al*, 2014	Autologous AMSCs	LDG: 1x10^7 MDG: 5x10^7 HDG:10x10^7	None	Intra-articular injection	None	3-4	None	(48)
Kim *et al*, 2014	Autologous AMSCs	3.9x10^6	AD	Implantation	Fibrin glue	1-2	MSCs vs. MSCs + fibrin glue	(49)
Randomized controlled trials								
Varma *et al*, 2010	Buffy coat	Not mentioned	None	Intra-articular injection	None	1-2	None	(50)

Table II. Continued.

Author, year	Number Origin of MSCs	of cells	Implementation Delivery system	method	Activation agent	K-L grade	Comparison	Ref.
Saw *et al*, 2013	Autologous PBSCs	NM	Microfracture injection	Intra-articular	None HA + PBSC group	NM	HA group vs.	(51)
Wang *et al*, 2013	Autologous BMAC	$1.46x10^7$	HTO injection	Intra-articular	HA vs. HTO group	NM	HTO + MSCs group	(52)
Vangsness *et al*, 2014	Allogenic BMSCs	$5.0x107,15x10^7$ meniscectomy	Partial medial injection	Intra-articular	None	NM	Group A: LD MSCs + HA Group B: HD MSCs + HA; control group: HA	(53)

MSCs, mesenchymal stem cells; PBSCs, peripheral blood stem cells; BMAC, bone marrow aspirate concentrate; BMSCs, bone marrow stem cell; K-L, Kellgren-Lawrence; PRP, platelet-rich plasma; GFAP, growth factor addition/preservation; LD, low-dose; HA, hyaluronic acid; HD, high-dose; HTO, high tibial osteotomy; AD, arthroscopic debridement; NM, not mentioned.

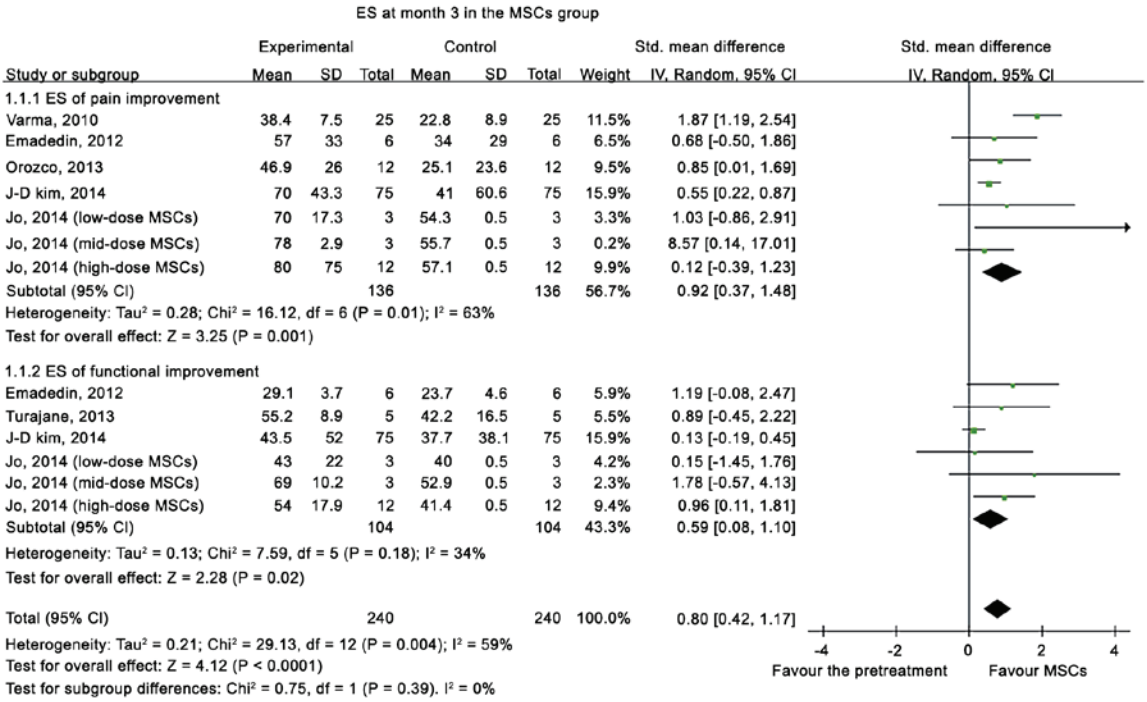
Results

Study characteristics. A total of 152 studies were initially searched, of which 117 were removed after title and abstract screening. Of the 35 citations, 18 clinical studies which met the inclusion criteria were identified for eligibility (Fig. 1); five case studies (17,22-26) were excluded and nine studies (24,27-34) were removed due to difficulties in extracting the outcome measurements. Four systematic reviews (35-38) were also excluded. An assessment of the remaining 18 studies revealed that 10 used a single-arm prospective design (18-20,39-45), four used quasi-experimental trials (46-49) and four used RCT (50-53) (Table I). A total of 565 participants (226 males and 339 females) were included from the 18 studies. The duration from the onset of knee pain to registration in each study was 3 months to ≥7 years. The follow-up period was 3-24 months. The majority of studies recruited patients with KOA with a severity grade of 1-4 on the K-L scale. K-L grade s 1-2, and grades 3-4 were defined as early OA and advanced OA, respectively (Table II).

Effects of MSCs. Compared with the pretreatment condition, a pooled ES of 0.80 (95%CI, 0.42-1.17) was determined at 3 months, 1.72 (95%CI, 1.13-2.31) at 6 months, 2.03 (95%CI, 1.30-2.76) at 12 months (Fig.2), and 1.81 (95%CI, 1.62-2.00) at 24 months (Fig. 3), which all favored the status after MSCs treatment. Following the exclusion of an outlier with an extremely high ES, the beneficial effects from MSCs treatment remained, with an ES of 0.77 (95%CI, 0.41-1.13) at 3 months, 1.49 (95%CI, 0.93-2.04) at 6 months, 1.63 (95%CI, 0.99-2.27) at 12 months, and 1.74 (95%CI, 1.55-1.93) at 24 months. A significant superiority of MSCs intervention was demonstrated by a high summed ES at 12 and 24 months without an overlap of the 95%CI of ES at 3 months, which indicated that the treatment effect of MSCs on KOA patients improved significantly over time. However, after excluding the data from quai-experimental and single-arm prospective studies and only using the data from RCTs, the treatment of MSCs did not demonstrate superiority. Relative to the baseline, patients improved in the pain and functional scale scores at all time points.

Stratified analysis. Participants receiving MSC treatment were stratified according to the study design, administration dosage, AD, activation agents and K-L grades. Point estimates of the pooled ES in the single-arm prospective studies and quasi-experimental trials were higher than those in the RCTs, and an uncertainty in the treatment effectiveness emerged regarding participants in the RCTs at 6, 12 and 24 months, since the 95%CI of the summed ES crossed the value of 0. Stratified analysis failed to demonstrate a dose-responsiveness association in the MSC numbers. However, the treatment effectiveness in the MSC groups with AD or activation agents was superior to the MSC groups without AD and activation agents, particularly at 12 months in the activation agents group (ES, 3.13; 95%CI, 1.55-4.71) compared with the group without activation agents (ES, 0.67; 95% CI, 0.01-1.34). And the early OA group exhibited a higher ES point estimate at all time points than the advanced OA group (Table III).

A



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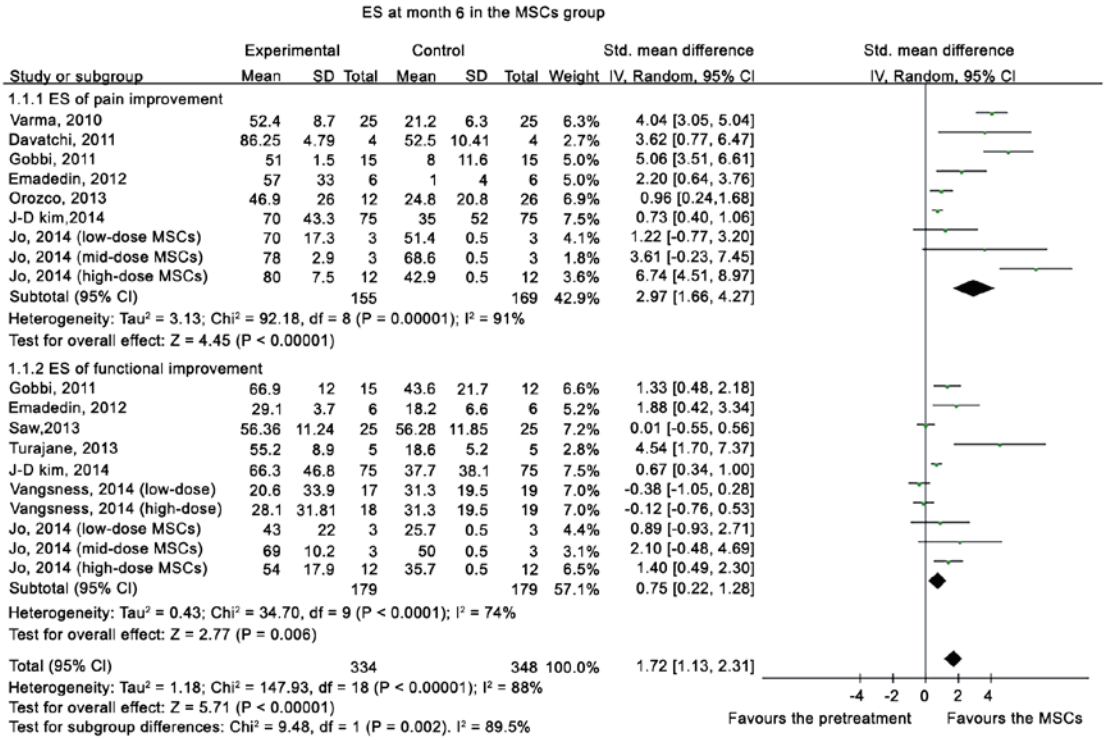

Figure 2. Forest plot of ES of pain and functional changes from baseline at (A) 3 and (B) 6 months after MSC treatment. ES, effect size; MSC, mesenchymal stem cell; SD, standard deviation; IV, inverse variance; CI, confidence interval.

Adverse effects and publication bias. Seven of the 18 trials reported adverse events after MSC treatment, in which the predominant symptoms were local swelling and transient regional pain. All of the adverse events reported by patients were self-limited or were remedied with therapeutic measures. None of the patients included in the present study were diagnosed with cancer that was associated with MSC therapy. Asymmetry was observed in the funnel plots based on the ESs of changes in the pain and functional scales from baseline (Fig. 4).

Discussion

The present meta-analysis comparing the conditions of patients with KOA before and after treatment with MSCs demonstrated a continual efficacy for at least 24 months.

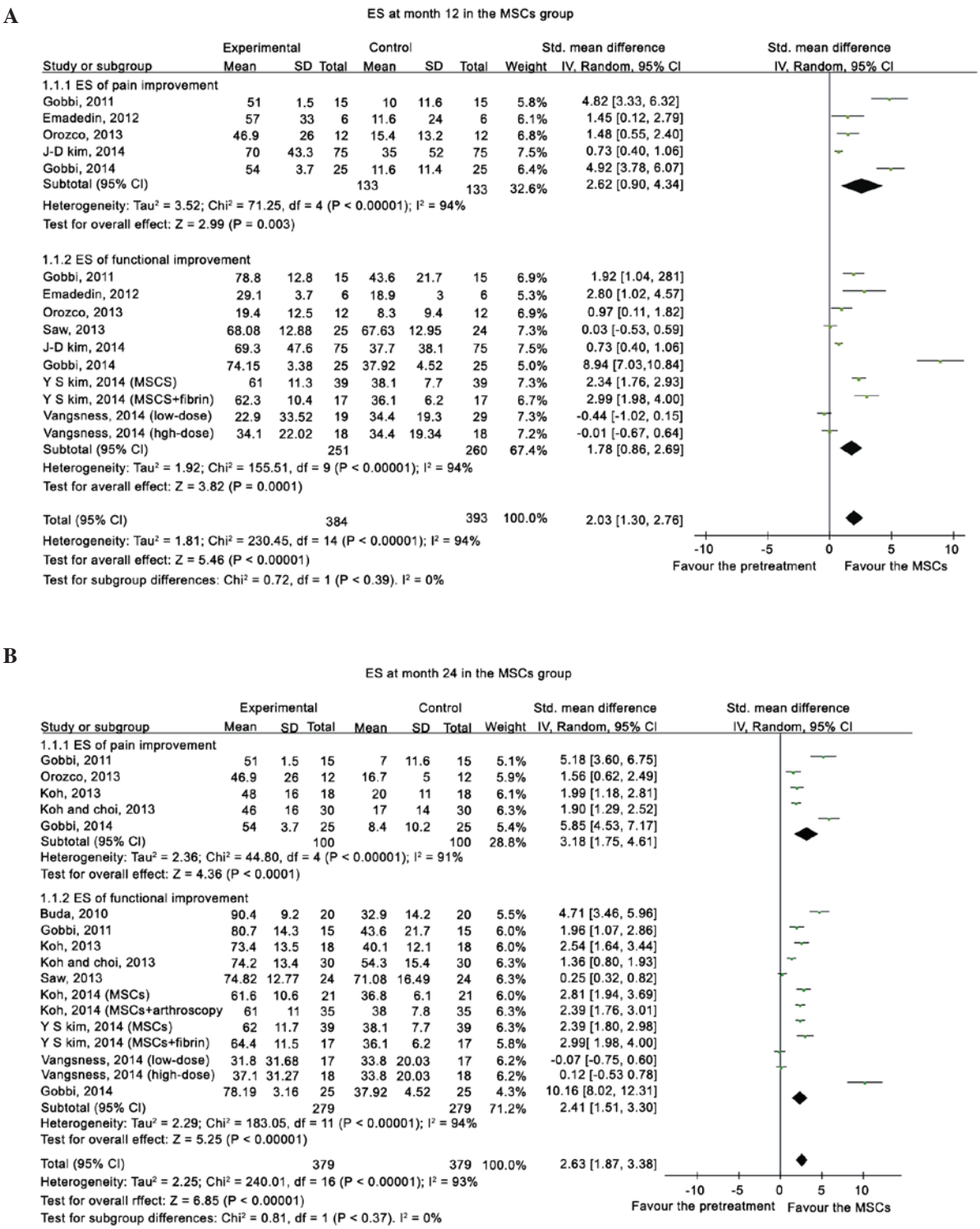

Figure 3. Forest plot of ES of pain and functional changes from baseline at (A) 12 and (B) 24 months after MSC treatment. ES, effect size; MSC, mesenchymal stem cell; SD, standard deviation; IV, inverse variance; CI, confidence interval.

Following analysis of the pooled ESs at 12 and 24 months, these values were higher than the summed ESs at 3 months, which indicated that the treatment effect of MSCs did not decrease in a time-dependent manner. However, a dose-responsiveness association was not demonstrated in the MSC numbers. The treatment effectiveness in the MSC groups treated with AD or activation agents was superior to the MSCs groups alone. Notably, the early OA group exhibited a higher ES point estimate at all time points, as compared with the advanced OA group.

To the best of our knowledge, no previous meta-analytic research has quantified the effectiveness of MSC treatment and analyzed the factors and modified the outcomes. Several reviews of the literature (35-38) have analyzed the role of MSCs therapy in KOA. Barry and Murphy (37) stressed that paracrine factor must be used as a measure to evaluate the

Table III. Analysis of the effect sizes of MSC treatment stratified by the indicated subgroups.

Subgroup	Pooled effect size at month 3	Pooled effect size at month 6	Pooled effect size at month 12	Pooled effect size at month 24
Study design				
Single-arm follow-up study	0.48 (0.18-0.77)	1.48 (0.51-2.44)	2.66 (1.69-3.62)	2.87 (1.99-3.75)
Quasi-experimental study	0.75 (0.17-1.32)	1.37 (0.59-2.14)	2.53 (1.96-3.10)	2.53 (2.18-2.89)
Randomized controlled trial	1.87 (1.19-2.54)	1.09 (-0.35-2.53)	0.14 (0.49-0.20)	0.12 (0.24-0.48)
MSCs doses administered				
$<5x10^6$	0.34 (-0.08-0.75)	0.70 (0.46-0.93)	1.60 (0.73-2.46)	2.25 (1.54-2.97)
$5x10^6$-$5x10^7$	0.89 (0.36-1.42)	1.39 (0.80-1.99)	1.60 (0.55-2.65)	-0.07 (-0.75-0.60)
$>1x10^7$	0.67 (0.09-1.26)	1.91 (0.58-3.23)	-0.01 (-0.67-0.64)	0.12 (-0.53-0.78)
Arthroscopic debridement				
Yes	0.37 (0.01-0.74)	0.45 (-0.16-1.06)	2.20 (1.30-3.09)	2.32 (1.61-3.03)
No	1.02 (0.58-1.47)	1.48 (0.80-2.16)	1.41 (0.83-2.00)	1.56 (0.62-2.49)
Activation agent				
Yes	0.37 (0.01-0.74)	1.40 (0.26-2.54)	3.13 (1.55-4.71)	2.82 (2.07-3.56)
No	1.02 (0.58-1.47)	1.29 (0.53-2.05)	0.67 (0.01-1.34)	0.84 (0.16-1.52)
Severity of degeneration				
Early OA	1.55 (0.66-2.45)	4.10 (3.16-5.04)	2.53 (1.96-3.10)	2.53 (2.18-2.89)
Advanced OA	0.78 (0.34-1.22)	2.40 (1.34-3.46)	1.99 (0.70-3.28)	2.54 (1.64-3.44)

Values are expressed by their point estimates with a 95% CI. 95% CI covered a zero value, which indicated an uncertainty of treatment effectiveness compared with the pretreatment baseline. MSC, mesenchymal stem cell; OA, osteoarthritis; CI, confidence interval.

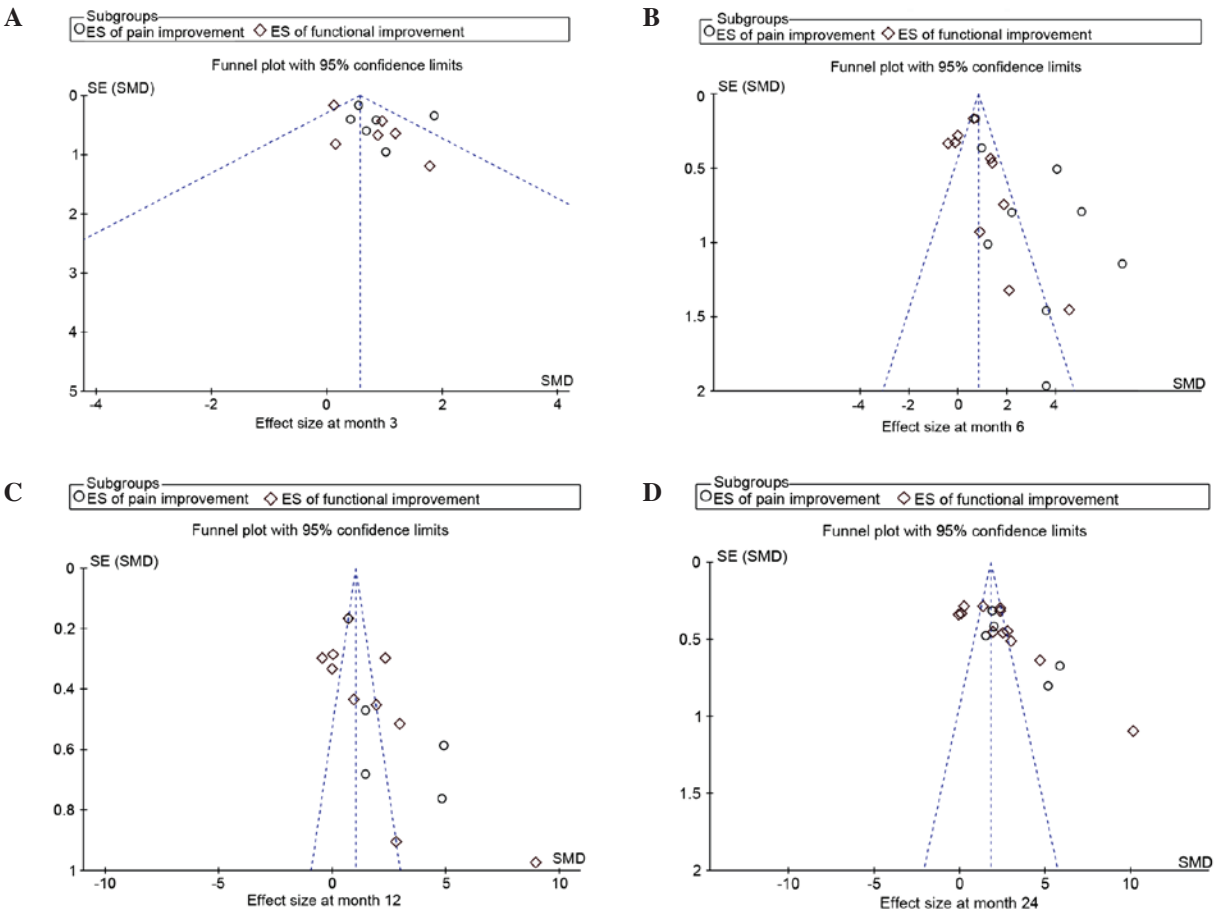

Figure 4. Funnel plots of the ES of pain and functional changes from baseline at (A) 3, (B) 6, (C) 12 and (D) 24 months post-MSC treatment. ES, effect size; MSC, mesenchymal stem cell; SE, standard error; SMD, standard mean difference.

potential treatment of MSCs in order to replace traditional measures based on differentiation and cell-surface markers. They also outlined that early-stage clinical trials are underway for test the method of intra-articular injection of MSCs into the knee. However, the optimal dose and vehicle have not been established. Filardo *et al* (38) reported that, due to the prevalence of low-quality preclinical studies and clinical trials, knowledge on the treatment of MSCs for cartilage regeneration remains preliminary, despite the growing interest in the biological approach. Rodriguez-Merchan (35) highlighted the efficacy of utilizing intra-articular injections of MSCs to treat KOA; however, the results of the treatment are simply encouraging. Kristjansson and Honsawek (36) discussed and assessed three ways in which MSCs may be used to treat OA patients by intra-articular injections and implantation as well as micro fracture. They reported that with higher numbers of MSCs injected superior results would be obtained. However, in order to facilitate the treatment, a single injection of MSCs alone or in combination of growth factors would be the ultimate solution.

The present meta-analysis suggested that MSC treatment significantly improved pain and functional status, relative to the basal evaluations in KOA, and the beneficial effect was maintained for two years after treatment. Furthermore, the treatment effectiveness did not reduce over time. Several factors mentioned by anecdotal research may modify the ESs of MSC treatment. In terms of the study design, the pooled ESs in single-arm and quasi-experimental studies were likely to be higher than those in RCTs. However, the results of these RCT studies suggested that MSCs also reduce pain and improve function in patients with KOA. Regarding the number of MSCs used in treatment, a dose-responsiveness relationship remained unclear. Jo *et al* (48) enrolled 18 patients who were injected with ADMSCs into the knee. The study consisted of three groups, the low-dose ($1.0x10^7$ cells), mid-dose ($5.0x10^7$), and high-dose ($1.0x10^8$) groups. However, a significant improvement in joint function and reduction in pain was observed in the low and mid-dose groups. Conversely, in previous studies, an increased number of cells yielded superior results. Therefore, the optimal dose and vehicle are yet to be established. One potential modifier is the AD. The present stratified analysis suggested that AD potentially contributed to an increase in treatment effectiveness. Another issue is the addition of activation agents, particularly at 12 months in the activation agents group (ES, 3.13; 95% CI, 1.55-4.71) compared with the group without activation agents (ES, 0.67; 95%CI, 0.01-1.34). The present subgroup analysis showed that the efficacy varied according to the degenerative severity, which was associated with the regenerative potential of damaged cartilage. These results are compatible with the findings of the majority of previous trials, and the early OA group exhibited a higher ES point estimated at all time points than the advanced OA group.

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