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Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials

Seong Hwan Kim[1] · Chul-Won Ha[2] · Yong-Beom Park[1] · Eunwoo Nam[3] · Jung-Eun Lee[3] · Han-Jun Lee[1]

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Abstract

Introduction Mesenchymal stem cells (MSCs) have gained popularity for articular cartilage repair. However, efficacy of intra-articular MSCs in osteoarthritis remains unclear. In the setting of a meta-analysis of randomized controlled trials (RCTs), we aimed to investigate the efficacy of intra-articular MSCs on clinical outcomes and cartilage repair in patients with knee osteoarthritis.
Materials and methods PubMed, EMBASE, Cochrane Library, CINAHL, and Scopus were searched from inception to March 31, 2017. This study included RCTs using cell population containing MSCs for treatment of knee osteoarthritis. The quality was assessed by Cochrane Collaboration`s risk of bias tool. For meta-analysis, data on clinical outcomes measured by visual analog scale (VAS), Lysholm score, WOMAC and data on cartilage repair measured by MOCART and WORMS were extracted. In studies with several cell concentrations, outcomes of recommended concentration were used mainly to ensure robustness.
Results A total of five RCTs (220 patients) were included. Two studies were deemed to have low risk of bias. In pooled analysis, there was significant difference in VAS score (mean difference [MD], −9.2; 95% CI: −17.21, −1.20) and Lysholm score (MD, 8.70; 95% CI 0.06, 17.34), but not WOMAC (MD, −7.44; 95% CI −20.38, 5.50). In cumulative functional analysis using Lysholm score and WOMAC in recommended concentration, there was a significant improvement (standard mean difference [SMD], 0.53; 95% CI 0.13, 0.94) after treatment. In cartilage repair assessed by MRI, there was no significant difference (SMD, 0.53; 95% CI−0.28, 1.34).
Conclusions This meta-analysis demonstrated that intra-articular MSCs have a limited evidence in pain relief and functional improvement in knee osteoarthritis. While MSCs may result in favorable clinical outcomes with a recommended concentration, use of concomitant treatment should be considered. In addition, current evidence does not support the use of intra-articular MSCs for improving cartilage repair in knee osteoarthritis.
Level of evidence Systematic review of Level-II studies.

Keywords Osteoarthritis · Mesenchymal stem cells · Clinical outcome · Cartilage repair · Meta-analysis

Seong Hwan Kim and Chul-Won Ha contributed equally.

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✉ Yong-Beom Park
whybe1122@gmail.com

[1] Department of Orthopedic Surgery, Chung-Ang University Hospital, Chung-Ang University College of Medicine, 102 Heukseok-ro, Dongjak-gu, 06973 Seoul, South Korea

[2] Department of Orthopedic Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, 06351 Seoul, South Korea

[3] Biostatistical Consulting and Research Lab, Medical Research Collaborating Center, Han-Yang University, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, South Korea

Introduction

Osteoarthritis is a common joint disease representing articular cartilage destruction, inflammation, and degeneration of other components of the joint [1]. Among these characteristics, cartilage destruction is a key feature that can lead to early osteoarthritis and advanced osteoarthritis. Currently, primary treatments for early to moderate osteoarthritis are palliative interventions including exercises, weight reduction, drugs or injection [2, 3]. In cases of moderate and advanced osteoarthritis where palliative interventions are insufficient, surgical intervention such as osteotomy or knee arthroplasty is performed as the last resort [2]. In this regard, a new therapeutic option needs to focus on reversing the pathophysiology of osteoarthritis including cartilage repair.

Recently, mesenchymal stem cells (MSCs) are emerging as potential treatment modalities for knee osteoarthritis due to their properties of self-renewal, multi-lineage differentiation potential, and immunomodulatory capacity [4, 5]. In addition, MSCs have shown a supporting effect on the healing process of the host through paracrine action [6, 7]. Endogenous MSCs in synovial fluid can be increased by aggression and inflammation to intra-articular tissues as a response to tissue injury [8, 9]. However, the number of available MSCs for cartilage repair is known to be scarce [10]. Therefore, administration of exogenous MSCs may meet the need to improve articular cartilage repair.

With an increasing interest in MSCs for treatment of knee osteoarthritis, many clinical studies have been conducted to evaluate the efficacy of MSCs on knee osteoarthritis in terms of pain and function. In addition, some review articles have evaluated the evidence of clinical application of MSCs for knee osteoarthritis [11–14]. However, clinical evidence of MSCs for knee osteoarthritis remains unclear. Although two articles have reported that MSCs could be safe and efficacious modality for knee osteoarthritis [11, 13], others have reported that MSCs for knee osteoarthritis have no clinical evidence, needing more studies with high-level evidence [12, 14]. However, some review articles have included non-randomized studies [12, 14] or domestic reports [11]. Moreover, some review articles mistook non-randomized study of Koh et al. [15] for randomized controlled study [11, 13]. This may result in controversial conclusion about MSCs for knee osteoarthritis. Thus, we intended to perform a meta-analysis to assess efficacy of intra-articular MSCs on knee osteoarthritis in terms of clinical outcome and cartilage repair with rigorous inclusion and exclusion criteria. This will provide more reliable information for proper understanding of current stem cell therapies for knee osteoarthritis by thorough review and analysis.

Materials and methods

This study was designed and conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. A full version of the protocol was registered on PROSPERO (CRD42018086416).

Data and literature sources

A comprehensive search of literature from several databases (PUBMED, EMBASE, the Cochrane Library, CINAHL and Scopus) was undertaken. The date was restricted to all publications by March 31, 2017. Search specifics were: "(Mesenchymal Stromal Cells"[Mesh] OR "mesenchymal stem cell*"[TIAB] OR "Stem Cells"[Mesh] OR "stem cell*"[TIAB]) AND ("knee"[Mesh] OR knee[TIAB]) AND ("Osteoarthritis"[Mesh] OR osteoarthritis[TIAB]). A manual search for additional eligible studies not found by the above search was performed for reference lists of included studies and relevant review articles. Articles identified were then assessed individually for inclusion.

Study selection

Studies presented in English language that assessed clinical outcome after administration of cell population containing MSCs in human with knee osteoarthritis were eligible. In vitro studies and animal studies were excluded. Randomized controlled trials (RCT) were included. Studies that did not include knee with osteoarthritis were excluded. The title and abstract of each publication were independently screened by two authors for eligibility. Subsequently, the same two authors individually performed full-text analysis. Disagreements about inclusion of a given study were solved by consensus between the two authors or consultation with the other author.

Data extraction

The above two authors independently recorded data from each study using a predefined data extraction form. Data on age, number of cases, follow-up, grade of osteoarthritis, site of source, source (autologous or allogeneic), methods and timing of delivery, culture expansion, entity of cells, number of cells, control intervention, and concomitant treatment were collected. Entity of cell population was clearly evaluated based on a consensus statement [17]. Outcome scales regarding pain and function were recorded for the following: visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), and Lysholm knee scale. In addition, Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) and Whole-Organ

Magnetic Resonance Imaging Score (WORMS) on MRI were extracted to evaluate cartilage repair.

Data analysis according to concentration of cells and definition of outcomes

In this meta-analysis, MSCs treatment groups from included studies were compared with their respective control groups. For each study, the mean value and standard deviation of outcomes were extracted according to concentrations of MSCs used in each study. Gupta et al. [18] and Lamo-Espinosa et al. [19] have compared results of multiple different concentrations of MSCs. Outcomes of recommended concentration of MSCs in their studies were used in this meta-analysis to ensure of the robustness results of this assessment. Additionally, average values of multiple outcomes from different concentration of MSCs were subjected to sensitivity analysis. Combined treatment effects for outcomes of pain and function as clinical categories were assessed via standardized mean differences. For those with negative effect direction, i.e., VAS and WOMAC, standardized mean difference (SMD), and 95% confident intervals (CIs) were converted into positive direction to be comparable with other indexes. The MRI evaluations were also assessed via SMD to standardize results of studies as a uniform scale, because Gupta et al. [18] and Lamo-Espinosa et al. [19] reported the results by WORMS scoring system, but Wong et al. [20] used the MOCART scoring system.

Assessment for risk of bias

It is well known that the inclusion of trials with a high risk of bias may pervert the results of a meta-analysis [16, 21]. Thus, the above two authors independently assessed the risk of bias using Cochrane Collaboration's risk of bias tool [21]. The possibility of publication bias was examined by Egger's test based on Galbraith plots [22]. Funnel plot asymmetry and Egger's tests were conducted to examine the possibility of publication bias. Since the total number of studies included in this meta-analysis was less than ten, the test for funnel plot asymmetry was inappropriate. Consequently, we treated the result from each single evaluation index as a trial and plotted a funnel plot via SMD. Similar to single evaluation indexes, the funnel plot asymmetry was assessed by treating the result from each evaluation index as a trial and unifying the effect direction. Disagreements were solved by consensus between two authors or in consultation with the other author.

Statistical analysis

Data analyses were performed with Review Manager software (version 5.3; Nordic Cochrane Centre, The Cochrane Collaboration). Statistical heterogeneity was assessed with I^2 statistics: $I^2 > 50\%$, substantial heterogeneity; $20\% < I^2 \leq 50\%$, moderate heterogeneity. A random-effects model was used because studies included in this analysis were assumed to be random samples of all possible studies thereby increase the risk of heterogeneity. Forest plots were used to show the outcome, pooled estimate of effect, and overall summary effect of each study. MSCs treatment effects were measured by mean differences (MDs) with 95% CIs if outcomes were measured in the same scale. On the other hand, when outcomes were assessed in distinct measures or scales, SMDs with 95% CIs were utilized to standardize results of studies to a uniform scale. $P < 0.05$ was considered statistically significant in all analyses. All reported P values were from two-sided version of respective test.

Results

Study characteristics

The selection process for studies is shown in Fig. 1. Four of these five studies were performed with bone marrow-derived mesenchymal stem cells (BM-MSCs) [18–20, 23] while the remaining one study was performed with adipose-derived stromal vascular fraction (ADSVF) containing adipose-derived MSCs (ASCs) [24]. Two studies performed concomitant surgery (high tibial osteotomy) [20, 24] while three studies used additional injections including platelet-rich plasma or hyaluronic acid [18, 19, 24]. Details of these included studies are summarized in Table 1.

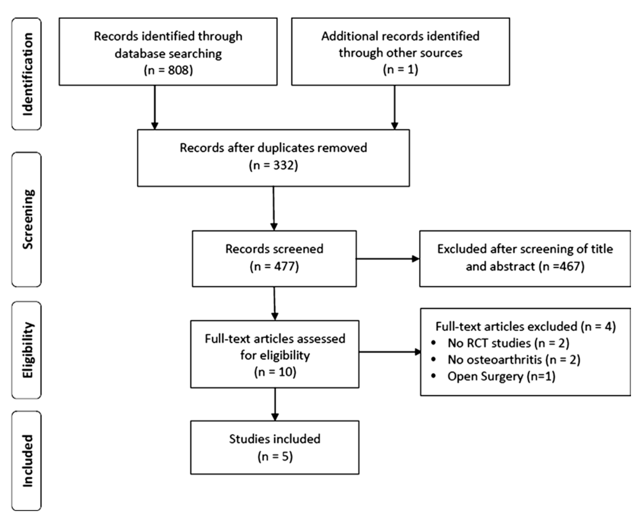

Fig. 1 Flow diagram of articles during selection process

Table 1 Details of included studies

Author (year)	Age	No. of cases	F-U (mon.)	OA grade	Source site	Source	Method and timing of injection	Culture expansion	Entity of cells	No. of cells	Control intervention	Concomitant treatment
Wong [20]	51	28 study 28 control	24	NS	BM	Autologous	Two-stage injection 3 weeks postoperatively	22 days	BM-MSCs	1.4×10^7	None	HTO, microfracture
Koh [15]	53	21 study 23 control	24	K–L less than 3	Adipose	Autologous	Direct injection, same day as arthroscopy	No, harvest at 1 day before surgery	ADSVF	4.83×10^7	None	HTO, PRP
Vega [23]	57	15 study 15 control	12	K–L 2 to 4	BM	Allogeneic	One-stage injection, same day as arthroscopy	22 days	BM-MSCs	4×10^7	HA	None
Gupta [18]	56	40 study 20 control	12	K–L 2 to 3	BM	Allogeneic	One-stage injection, same day as arthroscopy	21 days	BM-MSCs	$2.5–15 \times 10^7$	Placebo	HA
Lamo-Espinosa [19]	61	20 study 10 control	12	K–L 2 to 4	BM	Autologous	Two-stage injection 3–4 weeks after BM harvest	3–4 weeks	BM-MSCs	$1, 10 \times 10^7$	None	HA

F-U follow-up, *OA* osteoarthritis, *NS* not specified, *BM* bone marrow, *BM-MSCs* bone marrow-derived mesenchymal stem cells, *HTO* high tibial osteotomy, *K–L* Kellgren–Lawrence, *ADSVF* adipose-derived stromal vascular fraction, *PRP* platelet-rich plasma, *HA* hyaluronic acid

Assessment for risk of bias

Results of assessment for risk of bias on included studies are summarized in Fig. 2. Wong et al. [20], Koh et al. [24], and Lamo-Espinosa et al. [19] used autologous cells, which needs additional process to obtain MSCs. Thus, these studies were rated as having a high risk of performance or detection bias. Koh et al. [24] did not clearly report clinical outcomes nor specific scores, which was rated as having an additional high risk of attrition and reporting bias. Vega et al. [23] did not report all clinical outcomes including specific scores of WOMAC. Thus, the reporting bias for this study was rated as high. The funnel plot (Supplementary Fig. 1a) does not suggest publication bias in assessments by single evaluation index, including VAS, WOMAC, Lysholm knee scale, and MRI evaluations. Estimated effects were scattered within guidelines for 95% CI, which did not show asymmetrical distribution. Additionally, Egger's test found no significant publication bias ($P=0.133$). The funnel plot (Supplementary Fig. 1b) and the result of Egger's test also indicated the absence of publication bias in assessments by combined evaluation indices, including categories of functional and pain scores ($P=0.50$).

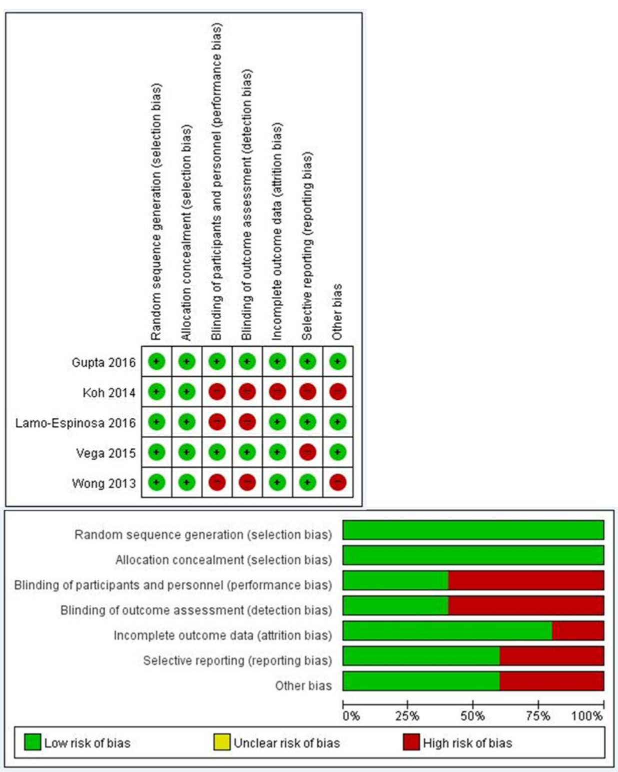

Fig. 2 Summary of the risk of bias assessment for included studies

Visual analog scale for pain (VAS)

VAS at final follow-up were described in four studies, including 114 patients (56 MSCs and 58 controls) [18, 19, 23, 24]. Three studies reported these scores at 12 months after surgery,[18, 19, 23] and one study reported these scores at 24 months after surgery [24]. VAS scores in MSCs treatment were significantly decreased (MD, −9.20; 95% CI: −17.21 to −1.20, $P=0.02$) compared with those in controls. Corresponding I^2 (41%) indicated moderate heterogeneity (Fig. 3a).

Western Ontario and McMaster Universities Osteoarthritis (WOMAC)

WOMAC at final follow-up were described in three studies [18, 19, 23], including 70 patients (35 MSCs and 35 controls). Because scales of WOMAC in Gupta et al. [18] were different from other studies [19, 23], we converted these scores to the same scale of WOMAC in other studies. MSC treatment led to decrease in WOMAC total scores with moderate heterogeneity ($I^2=33\%$), but it was not statistically significant (MD, −7.44; $P=0.26$) (Fig. 3b).

Lysholm knee scale

Two studies reported Lysholm knee scales [20, 24] (49 MSCs and 51 controls) with 24 months follow-up. Lysholm knee scales in MSCs treatment were significant increased (MD, 8.70; 95% CI: 0.06 to 17.34, $P=0.05$) compared to those in controls (Fig. 3c). The corresponding I^2 (61%) indicated substantial heterogeneity.

MRI evaluation

Three studies (96 patients) reported results of MRI evaluation (48 MSCs and 48 controls) [18–20]. MSC treatment led to improve results in MRI evaluation (SMD, 0.53, 95% CI: −0.28 to 1.34, $P=0.20$), but it was not statistically significant (Fig. 4). The corresponding I^2 (70%) indicated substantial heterogeneity.

Cumulative assessment of functional scores

Function scores of WOMAC and Lysholm of 140 patients (69 MSCs and 71 controls) were combined from four studies [18–20, 24]. Combined function scores in MSCs treatment were significantly increased (SMD, 0.53; 95% CI: 0.13 to 0.94, $P=0.01$) compared to those in controls

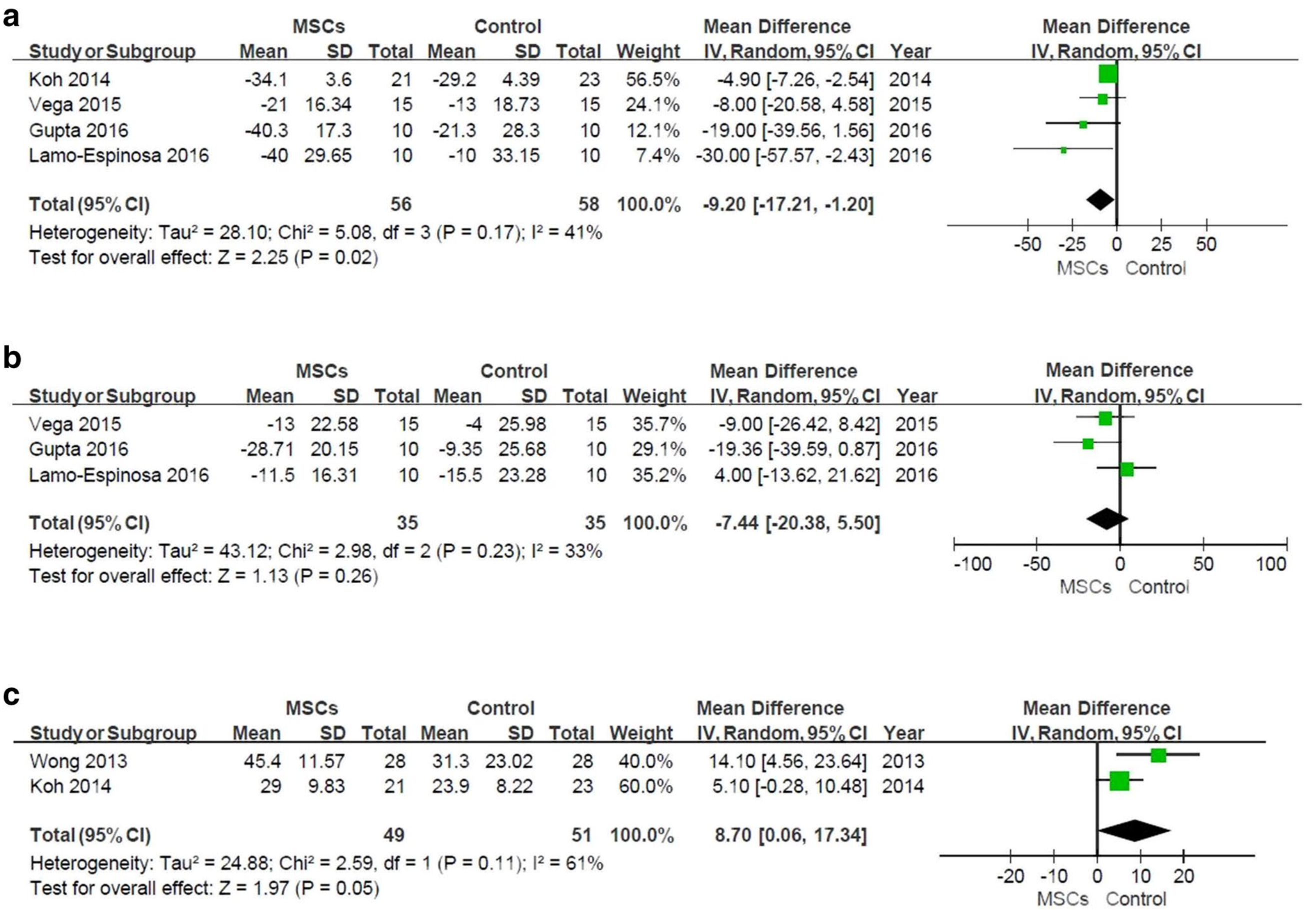

Fig. 3 Forest plots of mean difference with 95% confidence intervals in **a** VAS scores, **b** WOMAC total scores and **c** Lysholm knee scale between patients undergoing MSCs treatments and controls. Random-effect models were used. The green square represents results of each study. Ends of horizontal bars represent 95% confidence intervals. Black diamonds show overall results of all studies

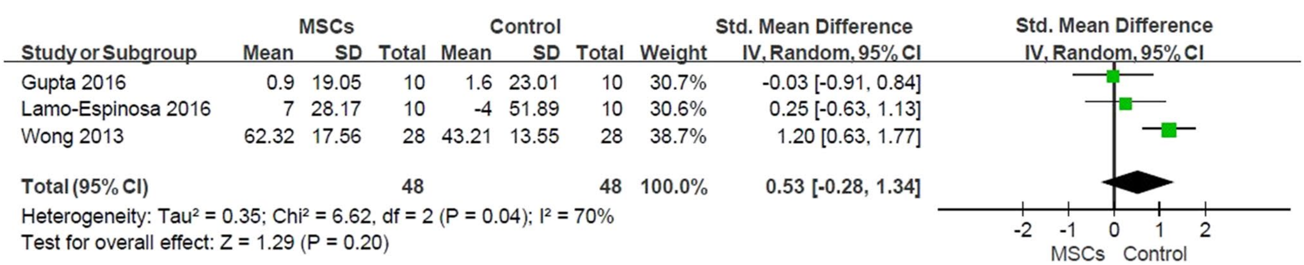

Fig. 4 Forest plots of standard mean difference with 95% confidence intervals in MRI evaluations between patients undergoing MSCs treatments and controls. Random-effect models were used

(Fig. 5a). Corresponding I^2 (25%) indicated moderate heterogeneity.

Cumulative assessment of pain scores

VAS pain scores from four studies [18, 19, 23, 24] and WOMAC pain scores from three studies [18, 19, 23] were used (184 patients; 91 MSCs and 93 controls). Combined pain scores in MSC treatment were significantly decreased (SMD, − 0.58; 95% CI: − 0.97 to − 0.19, $P = 0.004$) compared to those in controls (Fig. 5b). Corresponding I^2 (39%) indicated moderate heterogeneity.

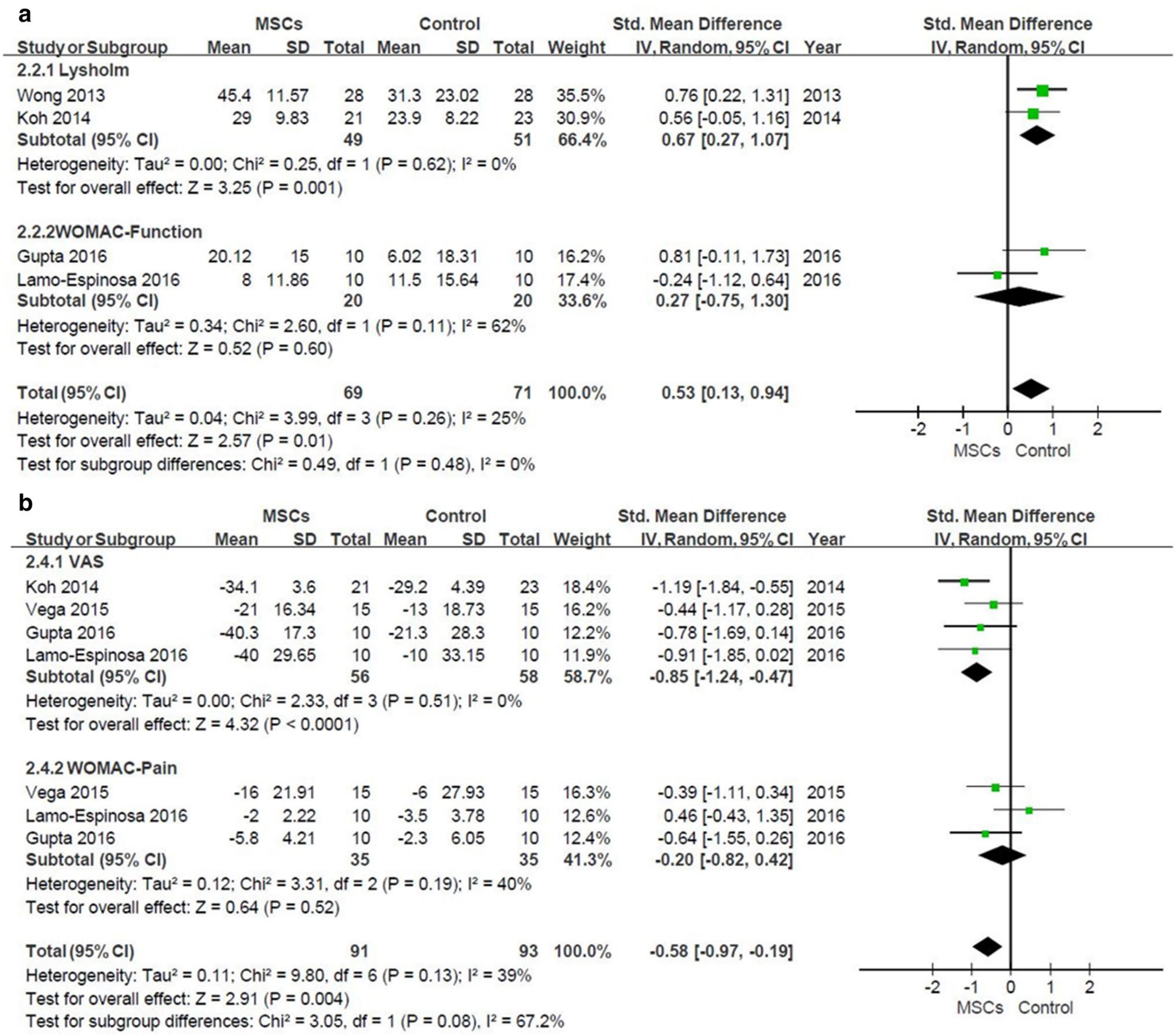

Fig. 5 Forest plots of standard mean difference with 95% confidence intervals in cumulative assessment of **a** functional scores (WOMAC function scores and Lysholm knee scale) and **b** pain scores (WOMAC pain scores and VAS scores) between patients undergoing MSCs treatments and controls. Random-effect models were used

Sensitivity analysis

We performed meta-analysis with average scores of multiple dosages for sensitivity analysis (Supplementary Figs. 2, 3, 4, 5, 6). Results from sensitivity analyses were similar to those from analyses with recommended dosages.

Discussion

Osteoarthritis of the knee is a very common, and there are various treatment modalities for it. However, in early and moderate stage of knee osteoarthritis, main treatment is a palliative. In this regard, a new therapeutic option needs to focus on reversing the pathophysiology of osteoarthritis including cartilage repair. In this meta-analysis, we found that application of MSCs with recommended concentration improved pain and function in short-term period of 12 or 24 months. However, intra-articular MSCs administration showed no clinical evidence for improving cartilage repair in knee osteoarthritis.

This meta-analysis revealed that intra-articular MSCs injection in knee osteoarthritis could significantly improve pain scores, including VAS scores and cumulative assessment of pain scores. VAS scores in MSCs treatment were significantly decreased compared with those in controls

($P = 0.02$), and the merge of three trials of WOMAC [18, 19, 23] and four trials of VAS scores [18, 19, 23, 24] also resulted in significant improvement in cumulative pain scores in short-term follow-up ($P = 0.004$). Sensitivity test using average values of multiple outcomes from different concentration of MSCs also showed similar results of the recommended concentration of MSCs. These findings indicate that intra-articular MSCs for knee osteoarthritis may be used for pain relief in short-term follow-up.

This meta-analysis showed that intra-articular MSCs injection could significantly improve functional outcomes in terms of Lysholm knee scale ($P = 0.05$), but not in WOMAC total scores ($P = 0.26$). [20, 24]. However, in cumulative assessment of functional scores of WOMAC function scores and Lysholm knee scales [18–20, 24], the SMD was found to be 0.53 which was statistically significant ($P = 0.01$). Sensitivity test results using average values of multiple outcomes from different concentration of MSCs were similar to those obtained using recommended concentrations of MSCs. These findings indicate that intra-articular MSCs injection with recommended concentration may improve functional outcomes in short-term follow-up.

In MRI evaluations, meta-analysis of three studies [18–20] showed no clinical evidence of improvement for cartilage repair. Three studies included in this meta-analysis showed different results [18–20]. One study reported that the MSC group showed no significant change from baseline to final follow-up without difference in terms of the WORMS score between groups [18]. Another study reported that despite improved WORMS scores at 6 months in all groups, scores were worse than baseline in the control and low-dose groups at 12 months while scores were maintained only in the high-dose group [19]. The other study reported improved cartilage status in the MSC group based on MRI evaluation at 12 months [20]. In the last study, HTO and microfracture were performed as adjuvant treatment at the time of MSCs injection. Although the efficacy of cartilage repair procedures with concomitant HTO was controversial, [25–27] intra-articular injection of MSCs after concomitant surgery showed significant high MOCART score than HTO and microfracture without MSCs injection [20]. However, in studies without adjuvant surgery, there was no significant improvement of cartilage status after intra-articular injection of MSCs [18, 19]. Therefore, we believe that well-designed studies of intra-articular injection of MSCs are necessary to accurately assess the efficacy of MSCs on cartilage repair in knee osteoarthritis.

This meta-analysis has some limitations. First, only studies with delivery methods of intra-articular injection were included for this review. Some studies performed open surgery for MSCs implantation for the treatment of knee osteoarthritis [28, 29]. Surgical implantation of MSCs may be more appropriate for cartilage repair. However, local administration of MSCs using injection seems to be logical because osteoarthritis is a whole joint disease, including articular cartilage degeneration, synovial hypertrophy, and inflammation [1]. Second, different stages of osteoarthritis of the knee joint were included in these studies. Especially, two studies included patients with K–L grade 4 of knee osteoarthritis [19, 23]. Reversing disease progression at advanced stage of knee osteoarthritis may be very difficult because problems of the knee joint in advanced stages are more complicated and destructive [30]. Nevertheless, results of this meta-analysis showed that intra-articular MSCs injections had favorable clinical outcome in terms of pain and function in knee osteoarthritis. We believe that specific criterion for the grade of knee osteoarthritis needs to be established for MSCs treatment in knee osteoarthritis. Third, several concomitant treatments including high tibial osteotomy, platelet-rich plasma, and hyaluronic acid injection were performed in conjunction with MSCs injection [31–34]. Although concomitant treatments themselves can improve pain and function in knee osteoarthritis, results of this review are derived from differences between MSCs with concomitant treatment and concomitant treatment without MSCs. Fourth, optimal cell concentration could not be determined due to heterogeneity of cell concentrations in these included studies [35–37]. Although a few studies assessed the results of cartilage repair according to the MSCs concentration, the results were inconsistent. Therefore, further study would be needed to determine the optimal cell concentrations.

Conclusion

Intra-articular MSCs have a limited evidence in pain relief and functional improvement in patients with knee osteoarthritis. While MSCs may result in favorable clinical outcomes with a recommended concentration, the use of concomitant treatment should be considered. In addition, current evidence does not support the use of intra-articular MSCs for improving cartilage repair in knee osteoarthritis. For clinical application of intra-articular injection of MSCs in knee osteoarthritis, further high-quality randomized trials that are methodologically rigorous and adequately powered with long-term follow-up are certainly warranted.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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