Intra-articular Injection of Mesenchymal Stem Cells After High Tibial Osteotomy

A Systematic Review and Meta-analysis

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Background: Multiple studies have investigated the use of mesenchymal stem cells (MSCs) for patients undergoing high tibial osteotomy (HTO), and the effectiveness thereof remains controversial.

Purpose: To analyze the effectiveness of intra-articular MSC injection in patients who underwent HTO in terms of clinical outcomes, radiological outcomes, and cartilage repair by a meta-analysis of the available literature.

Study Design: Systematic review; Level of evidence, 3.

Methods: The electronic databases of PubMed, Embase, Web of Science, and the Cochrane Library were searched from their inception to October 30, 2021, for comparative studies between patients who underwent HTO with and without intra-articular injection of MSCs, according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Study quality was assessed by the Coleman Methodology Score (CMS). Data with comparable results were pooled for meta-analysis. The primary outcomes of interest were the Hospital for Special Surgery (HSS), International Knee Documentation Committee (IKDC), Knee injury and Osteoarthritis Outcome Score (KOOS), and Lysholm scores, as well as the International Cartilage Regeneration & Joint Preservation Society (ICRS) grade of cartilage repair. Radiological outcomes including femorotibial angle, posterior tibial slope, and hip-knee-ankle (HKA) angle were included as secondary outcomes. A fixed-model effect was used for meta-analyses with low heterogeneity between studies ($I^2 < 25\%$), while the random-model effect was used for medium- to high-heterogeneity analyses ($I^2 \geq 25\%$).

Results: A total of 843 studies were screened, of which 6 studies with 452 patients met the inclusion criteria and were included. The mean CMS was 81.17. Patients with MSC injection had significantly higher Lysholm scores ($P = .007$) and HSS scores ($P = .01$) and higher proportions of ICRS grade 1 ($P = .03$) and grade 2 ($P = .02$) cartilage repair in the medial femoral condyle and grade 2 cartilage repair in the tibial plateau ($P = .04$). There were no significant differences between groups in the IKDC score, KOOS Pain and Symptoms subscales, femorotibial angle, posterior tibial slope, or HKA angle.

Conclusion: Intra-articular MSC injection may enhance the cartilage repair for patients who undergo HTO. However, evidence of improvement in knee functions remains limited.

Registration: CRD42021291345 (PROSPERO).

Keywords: mesenchymal stem cell; high tibial osteotomy; osteoarthritis; cartilage repair; meta-analysis

Maldistribution of weightbearing stress in the knee joint because of varus malalignment can increase the loading stress of the medial compartment, leading to progressive degeneration of the meniscus and cartilage and eventually medial compartmental knee osteoarthritis (OA). For younger patients with limited medial compartment OA, high tibial osteotomy (HTO), which is widely performed to delay the need for knee arthroplasty, can alleviate joint pain and improve quality of life. Recent studies have confirmed cartilage regeneration and satisfactory short- and medium-term results after HTO, because reduced medial compartment pressure may facilitate cartilage repair. However, because of the limited proliferation of hyaline cartilage, fibrocartilage is the major component of regenerate cartilage after HTO, and the deficiency of biomechanical properties of fibrocartilage compared with natural hyaline cartilage leads to an inevitable long-term failure. Therefore, additional cartilage repair procedures were suggested to enhance the outcomes of HTO.
Mesenchymal stem cells (MSCs) have been considered a feasible treatment for OA because of their potential in cartilage differentiation, immune regulation, and inflammatory suppression. Several studies have reported the good results of MSC injection in the treatment of OA. However, there is still a controversy over whether intra-articular MSC injection combined with HTO surgery can achieve better outcomes for medial compartment OA.

The purpose of this study was to systematically review the literature on the efficacy of intra-articular MSC injection for patients who underwent HTO. Our hypothesis is that intra-articular MSC injection could enhance the clinical outcomes and cartilage repair for patients who undergo HTO.

METHODS

This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and the protocol for the meta-analysis was registered with PROSPERO (CRD42021291345).

Search Strategy

The literature search was conducted independently by 2 authors (L.J. and G.Y.) across the PubMed, Embase, Web of Science, and Cochrane Library databases from their inception to October 30, 2021. The search consisted of 2 search strings, 1 of which was about stem cells (Medical Subject Headings: “mesenchymal stem cells” and “stem cells” and keywords “mesenchymal stem cells,” “mesenchymal stromal cells,” “MSCs,” “MSC,” “stem cells,” “stem cell”). The keywords for the other search string were “tibia,” “tibial,” “high,” “proximal,” and “osteotomy.” A combined search of 4 databases initially produced 843 results. Two independent authors (L.J. and G.Y.) screened the titles and abstracts of the combined search results and selected the qualified studies after removing duplicates. Subsequently, a full review of the qualified studies was then conducted according to the selection criteria. Any disagreements were resolved by discussion between the review authors or by consultation with a third author (J.D.).

Selection Criteria

The inclusion criteria were English-language studies evaluating clinical outcomes and/or cartilage repair after HTO, in which the experimental groups received intra-articular MSC injection and the control groups did not. Case reports with <5 patients and studies without specific clinical outcomes or results of cartilage repair were excluded.

Data Extraction

The following information was extracted: publication year, the name of the first author, level of evidence, sample size, sex ratio, mean patient age, mean follow-up, OA degree, interventions of groups, MSC details, primary outcomes, and secondary outcomes. The primary outcomes were functional scores (Hospital for Special Surgery [HSS], International Knee Documentation Committee [IKDC], Knee injury and Osteoarthritis Outcome Score [KOOS], and Lysholm score) and the results of cartilage repair, which was evaluated during second-look arthroscopic surgery. Radiological outcomes including the femorotibial angle, posterior tibial slope, and hip-knee-ankle (HKA) angle were included as secondary outcomes.

Quality Assessment

Two independent authors (L.J. and G.Y.) assessed the methodological quality of included studies using the Coleman Methodology Score (CMS) and reached a consensus through discussion. The CMS scoring system consists of 10 items, with the total score ranging from 0 to 100 (85-100, excellent; 70-84, good; 55-69, fair; <55, poor).

Statistical Analysis

Review Manager software (Version 5.4; Nordic Cochrane Centre, Cochrane) was used for data analysis. The heterogeneity of included studies was assessed with I² statistics (low heterogeneity, 0%-24%; moderate heterogeneity, 25%-75%; high heterogeneity, 76%-100%).
RESULTS

Study Selection

The literature search resulted in 843 studies. After removing duplicates (n = 227) and further screening by title and abstract, 6 studies were eligible for meta-analysis (Table 1). The literature search and selection process are shown in Figure 1.

Study Characteristics and Literature Quality Assessment

One of 6 studies used bone marrow–derived MSCs,36 while the other studies were performed with human umbilical cord blood–derived MSCs21,34,38 and adipose-derived MSCs.19,20 Three studies used allogenic MSCs,21,34,38 and the other 3 studies used autologous MSCs.19,20 Detailed characteristics of included studies are summarized in Table 1. The mean CMS was 81.17 ± 4.45 (Table 2). Four of 6 studies were of good methodological quality,21,34,36,38 while the other 2 studies were of excellent methodological quality.19,20

A fixed model effect was set as the default in every comparison. If moderate, moderate to high, or high heterogeneity was detected, a random model effect was used instead. Statistical significance was set at \( P < .05 \).

| Study          | LOE | N   | Sex, M/F | Mean Age, y | Mean BMI | K-L Grade | Follow-up, mo | MSC Group | Control Group | Clinical Outcomes | Radiological Outcomes | Second-Look Surgery |
|----------------|-----|-----|----------|-------------|----------|-----------|--------------|------------|---------------|--------------------|----------------------|----------------------|
| Kim (2018)19   | 3   | 100 | 68/32    | 58.8        | 26.7     | 3-4       | 38           | HTO + adipose MSC | HTO               | Lysholm, IKDC, others | FTA, PTS, others | Yes (ICRS)          |
| Koh (2014)20   | 2   | 44  | 33/11    | 53.4        | 25.2     | ≤3        | 24.4         | HTO + PRP + adipose MSC | HTO + PRP         | Lysholm, KOOS, VAS | FTA, others | Yes (other)         |
| Lee (2021)21   | 3   | 74  | 12/62    | 59.6        | 26.3     | NA        | 18.7         | HTO + hUCB-MSC | HTO+BMAC         | HSS, others | PTs, HKA, others | Yes (ICRS)          |
| Suh (2021)34   | 3   | 100 | 27/83    | 52.0        | 26.6     | NA        | 18           | HTO + hUCB-MSC | HTO+MFX          | Lysholm, IKDC, HSS | HSS                 | Others               | 1 patient |
| Wakitani (2002)36 | 2   | 24  | 15/9     | 63          | NA       | NA        | 16           | HTO + BM-MSC | HTO              | BMSC               | HSS                 | NA                   | Yes (other)         |
| Yang (2022)38  | 3   | 110 | 30/80    | 55.7        | 27       | 3         | 33           | HTO + hUCB-MSC | HTO+BMAC         | IKDC, KOOS, others | PTs, HKA, others | Yes (ICRS)          |

4BM, bone marrow; BMAC, bone marrow aspiration concentrate; BMI, body mass index; F, female; FTA, femorotibial angle; HKA, hip-knee-ankle; HSS, Hospital for Special Surgery; HTO, high tibial osteotomy; hUCB, human umbilical cord blood; ICRS, International Cartilage Regeneration & Joint Preservation Society; IKDC, International Knee Documentation Committee; K-L, Kellgren-Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; LOE, level of evidence; M, male; MFX, microfracture; MSC, mesenchymal stem cell; NA, not applicable; PRP, platelet-rich plasma; PTS, posterior tibial slope; VAS, visual analog scale.

Records identified through database searching (n = 843) Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 227)

Records excluded, with reasons:
1. No original data (n = 196)
2. Not human clinical trials (n = 206)
3. Not about knee OA (n = 173)
4. Not HTO and MSCs (n = 24)

Full-text articles included in quantitative synthesis (meta-analysis) (N = 6)

Studies included in quantitative synthesis (meta-analysis) (N = 6)

Figure 1. Process of study selection using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. HTO, high tibial osteotomy; MSC, mesenchymal stem cell; OA, osteoarthritis.
Clinical Outcome Analysis

Lysholm Score. The Lysholm score was reported in 3 studies with 244 patients (MSCs, n = 114; control, n = 130).20,34,38 One study reported Lysholm score at second-look arthroscopic surgery and the final follow-up,19 and the other 2 studies only reported the Lysholm score at the final follow-up.20,34 The Lysholm score in the MSC treatment group was significantly increased (mean difference [MD], 2.55%; 95% CI, 0.70-4.40; P = .007) as compared with the control group, with low heterogeneity (I² = 0%; Figure 2A).

IKDC Score. The IKDC score was reported in 3 studies with 310 patients (MSCs, n = 148; control, n = 162).19,34,38 One study reported the IKDC score at second-look arthroscopic surgery and the final follow-up,19 and the other 2 studies only reported them at the final follow-up.34,38 Treatment with MSCs led to an increase in IKDC score, with high heterogeneity (I² = 78%), although it was not statistically significant (MD, 4.81%; 95% CI, –0.23 to 9.84; P = .06) (Figure 2B).

Knee injury and Osteoarthritis Outcome Score. The KOOS was described in 2 studies including 154 patients (MSCs, n = 76; control, n = 78) at the final follow-up.20,38 The study by Koh et al20 only reported the Pain and Symptomatic subscales of the KOOS, while the study by Yang et al38 reported all subscales of the KOOS. Treatment with MSCs led to worsening in the Pain (MD, 4.15; 95% CI, –1.52 to 9.83) (Figure 2C) and Symptoms (MD, 3.53; 95% CI, –3.42 to 10.47) (Figure 2D) subscales of the KOOS, with high heterogeneity (Pain: I² = 83%; Symptoms: I² = 84%), although they were not statistically significant (Pain: P = .15; Symptoms: P = .32).

HSS Score. The HSS score was described in 3 studies including 198 patients (MSCs, n = 87; control, n = 111) at the final follow-up.21,34,36 The HSS score showed significant improvement in the MSC treatment group (MD, 4.33; 95% CI, 0.99-7.68; P = .01), with low heterogeneity (I² = 0%) compared with the control group (Figure 2E).

Radiological Outcomes

Femorotibial Angle (varus). The femorotibial angle was described in 2 studies with 144 patients (MSCs, n = 71; control, n = 73).19,20 Treatment with MSCs contributed to a decrease in femorotibial angle, with moderate heterogeneity (I² = 44%), although there was no statistical significance (MD, –0.35; 95% CI, –1.20 to 0.50; P = .42) (Figure 3A).

Posterior Tibial Slope. The posterior tibial slope was described in 3 studies including 284 patients (MSCs, n = 137; control, n = 147) at the final follow-up.19,21,38 Treatment with MSCs contributed to a decrease in posterior tibial slope, with no heterogeneity between studies (I² = 0%), although there was no statistical significance (MD, –0.35; 95% CI, –1.00 to 0.30; P = .29) (Figure 3B).

HKA Angle (valgus). The HKA angle was described in 2 studies including 184 patients (MSCs, n = 87; control, n = 97) at the final follow-up.21,38 Treatment with MSCs led to an increase in HKA angle (valgus), with no heterogeneity (I² = 0%), although the difference in outcomes was not statistically significant (MD, 0.10; 95% CI, –0.57 to 0.77; P = .77) (Figure 3C).

Second-Look Arthroscopy

Although good cartilage repair at second-look arthroscopic surgery was described by all included studies,19,21,34,36,38 the criteria for evaluation varied. Wakitani et al36 assessed cartilage repair using a modified arthroscopic grading scale, and hyaline-like cartilage covering defects was observed upon the second look. Suh et al34 only reported the arthroscopic view of 1 patient. Three studies assessed cartilage repair using the International Cartilage Regeneration & Joint Preservation Society (ICRS) grading system,19,21,38 of which reported ICRS scores of the medial femoral condyle and medial tibial plateau, respectively,19,21 while the other one only reported ICRS scores of overall cartilage.38 Thus, the 2 studies (82 patients) were included in this meta-analysis, and given the difference in the knee compartments, the data on the medial femoral condyle and medial tibial plateau were extracted and analyzed. Treatment with MSCs significantly increased the proportion of ICRS grade 1 (odds ratio [OR], 4.13; 95% CI, 1.12-15.26; P = .03) and grade 2 (OR, 2.38; 95% CI, 1.18-4.80; P = .02) cartilage repair in the medial femoral condyle and showed low heterogeneity (grade 1: I² = 13%; grade 2: I² = 0%) (Figure 4). Treatment with MSCs significantly increased the proportion of ICRS grade 2 cartilage repair (OR, 2.89; 95% CI, 1.07-7.79; P = .04) in the tibial plateau, with moderate to high heterogeneity (I² = 51%), which was not the same as the cartilage repair of the medial femoral condyle (Figure 5).

DISCUSSION

The main finding of this study was that treatment by MSC injection for patients who underwent HTO achieved better
cartilage repair compared with the control groups over a short-term follow-up. Cartilage repair assessed by ICRS grade demonstrated that treatment with MSCs significantly increased the proportion of grade 1 (OR, 4.13; \( P = .03 \)) and 2 (OR, 2.38; \( P = .02 \)) cartilage repair in the medial femoral condyle and grade 2 (OR, 2.89; \( P = .04 \)) cartilage repair in the tibial plateau. Although the MSC treatment significantly improved the Lysholm score (MD, 2.55; \( P = .007 \)) and HSS score (MD, 4.33; \( P = .01 \)) compared with the control group, the IKDC score (MD, 4.81; \( P = .06 \)), pain (MD, 4.15; \( P = .15 \)) and symptom (MD, 3.53; \( P = .32 \)) subscales of the KOOS, femorotibial angle (MD, –0.35; \( P = .42 \)), posterior tibial slope (MD, –0.35; \( P = .29 \)), and HKA angle (MD, 0.10; \( P = .77 \)) had no significant improvement. Therefore, intra-articular injection of MSCs is still controversial for improving the functional and radiological outcomes of patients who undergo HTO.

The merging analysis of 3 trials and the studies of Kim and Koh and Koh et al reported significant improvement in the Lysholm score after MSC injection for patients who underwent HTO; however, the study of Suh showed no significant improvement in the Lysholm score. Several studies reported significant improvement in the IKDC score after MSC injection; however, the merging analysis of 3 trials and the study of Yang showed no significant improvement in the IKDC score. Koh et al reported significant improvement on the Pain and Symptoms subscales of KOOS after MSC injection; however, the merging analysis of 2 trials showed no significant improvements with high heterogeneity in terms of the Pain and Symptoms subscales of KOOS (\( P = .15 \), \( I^2 = 83\% \); \( P = .32 \), \( I^2 = 84\% \)) (see Figure 2, C and D). The merging of 3 trials and the study of Lee et al reported a significant difference in HSS score after MSC injection.

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**Figure 2.** Forest plots detailing the mean difference in functional outcomes: (A) Lysholm score, (B) International Knee Documentation Committee score, (C) Knee injury and Osteoarthritis Outcome Score pain subscale, (D) KOOS symptom subscale, and (E) Hospital for Special Surgery score. IV, independent variable; MSC, mesenchymal stem cell.
compared with control groups; however, the studies of Suh et al\textsuperscript{34} and Wakitani et al\textsuperscript{36} showed no significant improvement in HSS score. These results suggest that the desired functional improvement in patients who undergo HTO may be difficult to achieve in patients who undergo intra-articular injection of MSCs compared with a control group.

In the evaluation of radiological outcomes, there was no evidence of improvement in terms of femorotibial angle, posterior tibial slope, and HKA angle in this meta-analysis. Kim and Koh\textsuperscript{19} reported that treatment with MSC injection led to no significant difference in femorotibial angle and posterior tibial slope after MSC injection compared with control groups. The study of Koh et al\textsuperscript{20} also reported no significant improvement of femorotibial angle. In the studies of Lee et al\textsuperscript{21} and Yang et al,\textsuperscript{38} posterior tibial slope and HKA angle were described, and there was no significant difference between the 2 groups. Some studies have reported that the radiological outcomes of the femorotibial angle and posterior tibial slope after HTO or total knee arthroplasty are closely related to the knee function.\textsuperscript{25,31,35} HKA angle, as a measurement of lower limb alignment, is associated with intra-articular load distribution and cartilage damage.\textsuperscript{12,28} Therefore, the results of this meta-analysis may suggest that the significant improvement of cartilage repair in patients who underwent HTO treated by MSC injection may not be the result of HTO surgery itself, but the repair effect of MSCs.

In evaluation of cartilage repair, the ICRS scores showed a significant improvement. Interestingly, although Kim and Koh\textsuperscript{19} and Lee et al\textsuperscript{21} reported that the intra-articular MSC injection contributed to a significant improvement of cartilage repair effects on the medial femoral condyle and medial tibial plateau in patients who underwent HTO, the results of this meta-analysis revealed that the cartilage repair of the medial femoral condyle was better than that of the medial tibial plateau. This study demonstrated that intra-articular injection of MSCs enhanced the proportion of grade 1 and 2 cartilage repair in the medial femoral condyle of patients who underwent HTO, while it only enhanced the proportion of grade 2 cartilage repair in the medial tibial plateau (see Figures 4 and 5). Without considering the difference in preoperative OA severity, the effect of MSC injection on the cartilage repair of the medial femoral condyle may be better than that of the medial tibial plateau.

### Strengths and Limitations

This study exhibited several strengths. First, the severity of OA in the patients who underwent HTO was similar among the included studies. The preoperative OA grade of patients who underwent HTO included in the 3 studies was Kellgren-Lawrence grade 3 OA.\textsuperscript{19,20,38} In the study by Wakitani et al,\textsuperscript{36} the preoperative OA of patients who underwent HTO was grade 1-2 as assessed by the Ahlback system,\textsuperscript{2} which is consistent with Kellgren-Lawrence grade 3.\textsuperscript{29} The other 2 studies,\textsuperscript{21,34} which did not directly describe the severity of OA in patients who underwent HTO, used ICRS scores to assess the extent of cartilage damage, ranging from grade 3B to grade 4, consistent with Kellgren-Lawrence grade 3 OA.\textsuperscript{1} Therefore, the similar OA degree of the patients who underwent HTO included in this meta-analysis made the evaluation of MSC injection for patients who underwent HTO more robust. Second, in the analysis
of cartilage repair, ICRS scores of the medial femoral condyle and medial tibial plateau were analyzed separately instead of the total ICRS scores of the entire knee joint, which enabled us to recognize the difference in cartilage repair of MSC injection on the medial femoral condyle and medial tibial plateau.

Limitations

This study has some limitations. First, the number of studies included was small, there was a lack of class I randomized controlled trials, and the level of evidence of the included studies was limited. Further inclusion of high-quality studies is needed to validate the conclusion of this meta-analysis, and the inconsistencies of the interventions used in our control group may have influenced our conclusions. Second, in 2 included studies of this meta-analysis, the bone marrow aspirate concentrate (BMAC) treatment group was considered as the control group. BMAC has a very low concentration of MSCs (0.001%-0.01%), as compared with culture-expanded, bone marrow–derived MSCs in vitro.30 According to the International Society for Cell Therapy, BMAC cannot be considered as MSCs because the differentiation of freshly isolated cells does not conform to the characteristics of trilineage differentiation.7 Therefore, although BMAC contains few MSCs, the BMAC treatment group can be regarded as the control group of MSC treatment because of the number of MSCs and the characteristics of cell differentiation.11 Third, 1 study included in this meta-analysis used platelet-rich plasma (PRP) in both the MSC and the control groups.18 The injection of PRP for patients with knee OA could improve knee function and cartilage repair, so inclusion of studies using PRP increases heterogeneity.4,8,10 However, given the use of PRP in both groups, the authors suggested that the difference in functional scores and cartilage repair between the 2 groups can be considered to be the effect of MSCs. Microfracture can also be used for cartilage defects and improve short-term clinical outcomes and cartilage repair.3,39 Suh et al34 used microfractures in the control group but not in the MSC treatment group, which also increased heterogeneity. Nonetheless, the MSC injection group showed a favorable IKDC score in the study of Suh et al.
CONCLUSION

Intra-articular MSC injection may significantly improve articular cartilage repair, especially for the medial femoral condyle compared with the medial tibial plateau. However, there is still controversy regarding the improvement of the functional outcomes of patients who undergo HTO.

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