Comparative Outcomes of Open-Wedge High Tibial Osteotomy With Platelet-Rich Plasma Alone or in Combination With Mesenchymal Stem Cell Treatment: A Prospective Study

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Purpose: This study compared the clinical results and second-look arthroscopic findings of patients undergoing open-wedge high tibial osteotomy (HTO) for varus deformity, with or without mesenchymal stem cell (MSC) therapy. **Methods:** This prospective, comparative observational study was designed to evaluate the effectiveness of MSC therapy. The patients were divided into 2 groups: HTO with platelet-rich plasma (PRP) injection only (n = 23) or HTO in conjunction with MSC therapy and PRP injection (n = 21). Prospective evaluations of both groups were performed using the Lysholm score, Knee Injury and Osteoarthritis Outcome Score (KOOS), and a visual analog scale (VAS) score for pain. Second-look arthroscopy was carried out in all patients at the time of metal removal. **Results:** The patients in the MSC-PRP group showed significantly greater improvements in the KOOS subscales for pain (PRP only, 74.0 ± 5.7; MSC-PRP, 81.2 ± 6.9; $P < .001$) and symptoms (PRP only, 75.4 ± 8.5; MSC-PRP, 82.8 ± 7.2; $P = .006$) relative to the PRP-only group. Although the mean Lysholm score was similarly improved in both groups (PRP only, 80.6 ± 13.5; MSC-PRP, 84.7 ± 16.2; $P = .357$), the MSC-PRP group showed a significantly greater improvement in the VAS pain score (PRP only, 16.2 ± 4.6; MSC-PRP, 10.2 ± 5.7; $P < .001$). There were no differences in the preoperative (PRP only, varus 2.8° ± 1.7°; MSC-PRP, varus 3.4° ± 3.0°; $P = .719$) and postoperative (PRP only, valgus 9.8° ± 2.4°; MSC-PRP, valgus 8.7° ± 2.3°; $P = .678$) femorotibial angles or weight-bearing lines between the groups. Arthroscopic evaluation, at plate removal, showed that partial or even fibrocartilage coverage was achieved in 50% of the MSC-PRP group patients but in only 10% of the patients in the PRP-only group ($P < .001$). **Conclusions:** MSC therapy, in conjunction with HTO, mildly improved cartilage healing and showed good clinical results in some KOOS subscores and the VAS pain score compared with PRP only. **Level of Evidence:** Level II, prospective comparative study.

Globally, osteoarthritis (OA) is the most common cause of knee pain. Arthritis of the knee joint commonly affects the medial compartment and is associated with misalignment, thereby placing a greater load on the affected compartment.[1] High tibial osteotomy (HTO) is a treatment option for younger and/or physically active patients who have OA of the medial compartment of the knee. HTO was originally devised to treat varus OA by decreasing pressure on the medial compartment.[2] In this regard, several studies have reported remodeling of the articular cartilage after HTO and attributed improvements to reduced contact stress by altering the weight-bearing axis.[2-5] However, HTO alone induces partial remodeling of the articular cartilage,[3] and therefore additional procedures, such as stem cell transplantation, may further enhance articular cartilage healing in OA patients.

Intra-articular injection of mesenchymal stem cells (MSCs) was reported to be effective for reducing pain in patients with knee OA.[6,7] In a previous study, post-operative magnetic resonance imaging studies also showed notable improvements in medial femoral condyle cartilage defects. On the basis of these findings, stem cell injection was used to achieve greater cartilage remodeling and better clinical results after HTO surgery.

The purpose of this study was to compare the clinical results and second-look arthroscopic findings in patients undergoing open-wedge HTO for varus deformities, with or without MSC therapy. MSC

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therapy with platelet-rich plasma (PRP), in conjunction with HTO, was hypothesized to provide improved cartilage healing and clinical results compared with injection of PRP only.

Methods

This prospective, comparative observational study was designed to evaluate the effectiveness of MSC therapy. Study protocols were approved by the local ethics committee, and all patients provided written informed consent. From January to October 2011, 44 patients who met the following inclusion criteria were enrolled in this study. The inclusion criteria for surgical treatment reflected those outlined in the literature for this procedure: (1) age younger than 60 years, (2) radiographs showing grade III or lower Kellgren-Lawrence symptomatic isolated medial knee compartment OA, (3) failure of conservative treatment, and (4) absence of additional cartilaginous procedures (autologous chondrocyte transplantation, microfracture). Patients were excluded if they did not consent to undergo a second operation for plate removal and second-look arthroscopy and could not be evaluated at either the 1- or 2-year postoperative visit. In addition, patients were excluded if they had undergone previous cartilage procedures, such as microfracture or chondroplasty, for chondral lesions of the medial femoral condyle because the intention was to examine the effect of MSC therapy on cartilage healing. Patients were also excluded if they met at least 1 of the following criteria: severe cartilage lesions of the lateral compartment or patellofemoral compartment, as observed using preoperative magnetic resonance imaging; inflammatory or postinfectious arthritis; previous arthroscopic treatment for knee OA; previous major knee trauma; intra-articular hyaluronic acid or corticosteroid injection within the preceding 3 months; mechanical pain caused by meniscal tears (including flap tears, bucket-handle tears, and complex tears); chronic anterior cruciate ligament/posterior ligament instability; or inability to provide informed consent.

Patients were randomized into either the PRP-only group or the MSC-PRP group. Simple randomization methods were used in which each patient, when enrolled in the trial, was asked to choose either of 2 identical envelopes with either the PRP-only or MSC-PRP group indicated inside. The randomization process was conducted by a hospital staff member blinded to the patients' data. Patients, however, were not blinded to the interventional method (liposuction) used. A total of 52 patients were enrolled, with 26 knees comprising each group.

The patients were prospectively evaluated by physiotherapists using the Lysholm score,[8] the Knee Injury and Osteoarthritis Outcome Score (KOOS),[9] and a 100-point visual analog scale (VAS) score for pain (0, no pain; 100, worst possible pain). Patients were evaluated preoperatively and postoperatively at 3 months, at 1 year, and at the last follow-up visit (mean, 24.4 months; range, 24 to 25 months). Before surgery, radiographs of the knee joints were obtained, including an anteroposterior (AP) view, a true lateral view at 30° of knee flexion, and an AP long-leg weight-bearing view. To investigate the mechanical effects of HTO, the femorotibial angle (FTA) and percentage of mechanical axis[10] were measured using standing AP radiographs taken immediately before surgery and after surgical removal of the plate. The FTA was determined as the angle between the femoral and tibial shaft axes on the standing AP radiographs.

Collection of Subcutaneous Adipose Tissue

Subcutaneous adipose tissue was harvested from both buttocks of each patient. One day before HTO, adipose tissue was harvested by tumescent liposuction, with the patient under local anesthesia.[11] Routinely, 140 mL of adipose tissue that had undergone liposuction was collected; 120 mL was used for the injection. The remaining 20 mL was subjected to laboratory analyses to assess the plastic-adherent cells that formed colony-forming unit fibroblasts and to confirm the multilineage differentiation of the adipose-derived stem cells (ADSCs).

Isolation of Stromal Vascular Fraction and MSCs From Subcutaneous Adipose Tissue

In the operating room, adipose tissue (120 mL) was suspended in phosphate-buffered saline solution, placed in a sterile box, and transported to a laboratory. Mature adipocytes and connective tissue were separated from the stromal vascular fraction (SVF) by centrifugation, as reported by Zuk et al.[12] The volume of the SVF was usually less than 1.0 mL. For injection, SVF cells were prepared with approximately 3.0 mL of PRP. Before injection, bacteriologic tests were performed to ensure the absence of sample contamination, and the cell viability was assessed by methylene blue dye exclusion.

Assessment of Plastic-Adherent Cells That Form Colony-Forming Unit Fibroblasts and Immunophenotyping of ADSCs

To evaluate the frequency of mesenchymal-like progenitors in patients' SVF, cells were cultured in T-25 flasks at a final concentration of 16 cells/cm^2. Colonies consisting of 50-cell aggregates or greater were scored under an optical microscope, and the immunophenotypes of the ADSCs were analyzed by flow cytometry (fluorescence-activated cell sorting). MSC marker phenotyping was performed as previously described.[13]

Confirmation of Multilineage Differentiation of ADSCs

ADSCs were plated at 2×10^3 cells/cm^2 in Dulbecco's modified Eagle medium containing 10% fetal bovine

serum and allowed to adhere for 24 hours. The culture medium was then replaced with specific media to induce adipogenic, osteogenic, and chondrogenic differentiation, as previously reported.[13]

PRP Preparation

For PRP preparation, a 60-mL venous blood sample (collected in a tube containing 4 mL of sodium citrate) was collected from each patient. A complete peripheral blood count was determined. The samples were centrifuged twice (at 1,800 rpm for 15 minutes to separate the erythrocytes and then at 3,500 rpm for 10 minutes to concentrate the platelets) to yield 6 mL of PRP. The PRP was divided into 2 units of 3 mL each. One unit was sent to the laboratory for determination of the platelet concentration and for quality testing (bacteriologic tests); the other was used for the first injection, within 2 hours of preparation.

MSC Implantation and Open-Wedge HTO

The patients were positioned supine on the operating table, and a thigh tourniquet was applied. Before undergoing HTO, each patient underwent arthroscopic surgery. Using arthroscopy, the orthopaedic surgeons (Y-G.K., Y-J.C.) evaluated the medial, lateral, and patellofemoral joint compartments; graded the articular lesions according to the International Cartilage Repair Society Cartilage Injury Evaluation Package[14]; irrigated the compartment with at least 1 L of saline solution; and performed 1 or more treatments, including synovectomy, debridement or excision of the degenerative tears of the menisci, or removal of articular cartilage fragments, chondral flaps, or osteophytes that prevented full extension. After completion of the arthroscopic procedure, the arthroscopic fluid was washed out. In the MSC-PRP group, injection of MSCs plus PRP (isolated 1 day before arthroscopic surgery) was administered under arthroscopic guidance. In the PRP-only group, the injection of PRP alone was performed after the arthroscopic procedure by injection into the medial joint space under arthroscopic guidance.

After injection, HTO was performed according to the technique recommended by the AO International Knee Expert Group.[15] The TomoFix system (Synthes, Solothurn, Switzerland) was used to stabilize the osteotomy, which was performed in a biplanar fashion. Before surgery, the correction angle and open-wedge size were calculated by the operator (Y-G.K. and Y-J.C.), using AP radiographs of the lower extremity (orthoroentgenogram) with the patient in standing (full weight-bearing) position. The aim was to pass the weight-bearing line through a point 62% lateral to the tibial plateau from the medial edge of the medial tibial plateau; the correction angle and size of the open wedge were measured on the orthoroentgenogram before surgery. All measurements were independently calculated by 2 junior surgeons (O-R.K., Y-S.K.), and all osteotomies aimed for mild overcorrection.[16] A β−tricalcium phosphate (Synthes, Bettlach, Switzerland) wedge, corresponding to the open space, was inserted into the osteotomy site. This material is a fully synthetic, resorbable bone graft substitute, consisting of pure β−tricalcium phosphate with a compressive strength similar to that of cancellous bone.

One day after surgery, isometric quadriceps, active ankle, and straight leg−raising exercises began. The patients were allowed to move their knee from 0° to 90° after 2 weeks. Toe-touch weight bearing was allowed for 2 weeks after surgery, followed by partial weight bearing for the next 2 weeks. Full weight bearing was allowed at 4 weeks, after radiographic evaluation of bone consolidation at the osteotomy site.

Second-Look Arthroscopy

For all patients in this study, second-look arthroscopy was performed during metal removal for fixation. The interval between HTO (first intra-articular observation) and removal of the plate (second intra-articular observation) was 14 to 24 months (mean, 19.8 months). All second-look arthroscopies were video recorded (3 to 5 minutes). The examinations were performed during second-look arthroscopy video review by all members of the surgical team, and the findings were confirmed only when a consensus was reached. Chondral lesions were described, according to the Kanamiya grading system,[4] as follows: grade 1, no regenerative change; grade 2, white scattering with fibrocartilage; grade 3, partial fibrocartilage coverage; and grade 4, even fibrocartilage coverage.

Power Calculation and Statistical Analysis

A difference of 15 points in the Lysholm score (1 of the main outcome measures) represented a clinically significant difference between treatment groups. Thus, accepting less than 5% probability of a type I error and a power of 80%, we determined that a total sample size of 22 patients was required for each group. Predicting a 10% dropout rate, we enrolled a total of 52 patients, with 26 knees comprising each group.

Statistical analyses were performed by use of SPSS software, version 12.0.1 (SPSS, Chicago, IL), with significance defined as $P < .05$. The principal dependent variables of the clinical outcomes were the KOOS, Lysholm score, and VAS pain score at the final follow-up. The Fisher exact test and a χ^2 test were used to compare categorical data. Differences between groups were analyzed by use of the Mann-Whitney U test. The Wilcoxon rank sum test was used for within-group analyses (preoperative *v* postoperative in same group). The Spearman rank order correlation test was used to

Table 1. Overview of Patient Groups

	PRP-Only Group	MSC-PRP Group	*P* Value
No. of patients	23	21	
Male/female sex (n)	6/17	5/16	.53
BMI (kg/m^2)	24.7 ± 3.3	25.7 ± 2.9	.29
Follow-up period (mo)	24.6 ± 6.4	24.2 ± 4.7	.32
Age (yr)	52.3 ± 4.9	54.2 ± 2.9	.48

NOTE. Values are expressed as mean ± standard deviation unless otherwise indicated.
BMI, body mass index.

analyze the correlation between cartilage healing status and patient demographic factors.

Results

Patient Characteristics

The patient demographic data and characteristics are shown in Table 1. Figure 1 shows the trial profile of this study. There were 52 patients recruited into the study, 26 patients in each group. However, 5 patients (2 in the PRP-only group and 3 in the MSC-PRP group) could not be evaluated at either the 1- or 2-year post-operative visit. Second-look arthroscopic data are missing for 1 patient in the PRP-only group and for 2 patients in the MSC-PRP group because they did not consent to undergo a second surgical procedure for plate removal. Finally, for 44 patients (23 in the PRP-only group and 21 in the MSC-PRP group), second-look arthroscopic results and 2-year clinical results were available for the last analysis. There were no significant differences in patient demographic data between the 2 groups.

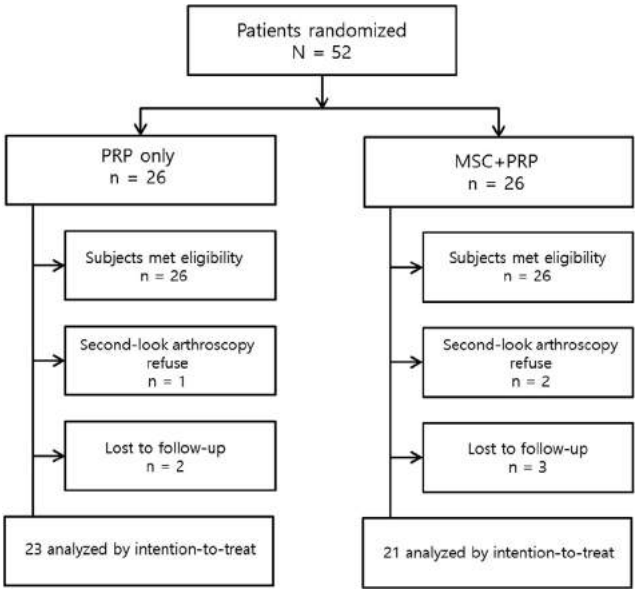

Fig 1. Trial profile of patients randomized in study. The patients were randomized into 2 groups of 26 subjects each; 5 patients were lost to follow-up during the 2-year follow-up and 3 patients refused the second-look arthroscopy.

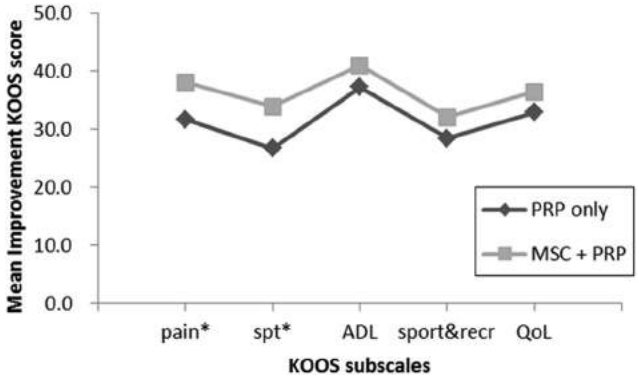

Fig 2. Mean improvement from baseline in KOOS subscales at last follow-up. Asterisks indicate statistical significance ($P < .05$). (ADL, activities of daily living; QOL, quality of life; sports&rec, sports and recreation; spt, symptoms.)

Cell Isolation and Characterization of ADSCs

The platelet concentrations (mean ± SD) in whole blood and PRP were 208.53 ± 42.9 × 10^3/mL and 1,303.27 ± 375.2 × 10^3/mL, respectively.

After isolation, ADSCs represented 8.5% of the SVF cells (range, 6.8% to 10.2% of SVF cells), or 4.11 × 10^6 stem cells (8.5% of the 4.83 × 10^7 SVF cells) were prepared. Flow cytometry characterization showed positive expression of the CD90 (98.34%) and CD105 (91.23%) surface markers and negative expression of CD45 (2.23%), CD34 (6.45%), and CD14 (2.32%). ADSCs treated with conditioned media showed characteristics of adipogenic, osteogenic, and chondrogenic differentiation, as previously reported.[17]

Clinical and Radiologic Outcomes at Follow-up

The patients in the MSC-PRP group showed a trend toward greater improvements in all of the KOOS subscales, although significant differences were only observed for the pain and symptom subscales at the last follow-up (Fig 2). The MSC-PRP group showed significantly greater improvements in the KOOS pain subscale (PRP only, 74.0 ± 5.7; MSC-PRP, 81.2 ± 6.9; $P < .001$) and symptom (PRP only, 75.4 ± 8.5; MSC-PRP, 82.8 ± 7.2; $P = .006$) scores relative to the PRP-only group. The other clinical and radiologic outcomes at the preoperative and final follow-up time points, for both groups, are summarized in Table 2. The mean Lysholm score was also significantly improved in both groups ($P < .001$), but no differences were seen between the groups ($P = .357$). Although the mean VAS pain score decreased significantly (i.e., improved) at the final follow-up visit in both groups ($P < .001$), the MSC-PRP group showed a greater improvement relative to the PRP-only group ($P < .001$).

The standing AP radiographs taken immediately after implant removal showed improved knee joint mechanics in both groups relative to their preoperative conditions. However, there were no differences in the

Table 2. Clinical and Radiologic Results of Patient Groups

	PRP-Only Group	MSC-PRP Group	*P* Value (95% CI)
Lysholm score			
Preoperative	56.7 ± 12.2	55.7 ± 11.5	.747 (−12.12 to 8.83)
Last follow-up	80.6 ± 13.5	84.7 ± 16.2	.357 (−8.4 to 1.2)
VAS			
Preoperative	45.4 ± 7.1	44.3 ± 5.7	.460 (−0.77 to 0.29)
Last follow-up†	16.2 ± 4.6	10.2 ± 5.7	<.001 (0.23 to 0.98)
WBL (%)			
Preoperative	16.1 ± 5.7	17.7 ± 7.3	.800 (−2.56 to 3.91)
Last follow-up	60.3 ± 3.0	61.1 ± 3.4	.758 (−3.50 to 4.51)
FTA (°)			
Preoperative	Varus 2.8 ± 1.7	Varus 3.4 ± 3.0	.719 (−1.30 to 1.87)
Last follow-up	Valgus 9.8 ± 2.4	Valgus 8.7 ± 2.3	.678 (−1.32 to 1.90)
Initial cartilage status (n)*			.876
Grade 2	1	0	
Grade 3	11	9	
Grade 4	11	12	

NOTE. Values are expressed as mean ± standard deviation unless otherwise indicated.
CI, confidence interval; WBL, weight-bearing line.
*Initial cartilage status was graded by arthroscopy before HTO; the orthopaedic surgeons (Y-G.K., Y-J.C.) evaluated the medial joint compartments and graded the articular lesions according to the International Cartilage Repair Society Cartilage Injury Evaluation Package.
†Significant difference at last follow-up between groups ($P < .05$).

postoperative FTAs ($P = .678$) or weight-bearing lines ($P = .758$) between the groups.

Second-Look Arthroscopy

There were no significant differences in the initial cartilage status between the groups ($P = .876$) (Table 2). However, there was a significant difference between the groups with respect to cartilage healing ($P = .023$) (Fig 3). Second-look arthroscopy, during plate removal, showed that 0 of the 23 knees in the PRP-only group had even fibrocartilage coverage (grade 4), determined arthroscopically. One knee (4.3%) had partial fibrocartilage coverage (grade 3), 11 (47.8%) had white scattering with fibrocartilage (grade 2), and 11 (47.8%) did not show any regenerative changes (grade 1). In contrast, in the MSC-PRP group, 3 knees (14.3%) had even fibrocartilage coverage (grade 4), 8 (38.1%) had partial fibrocartilage coverage (grade 3), 9 (42.9%) had white scattering with fibrocartilage (grade 2), and 1 (4.8%) did not show any regenerative changes (grade 1). Figure 4 shows examples of the arthroscopic photographs used in the patient evaluations.

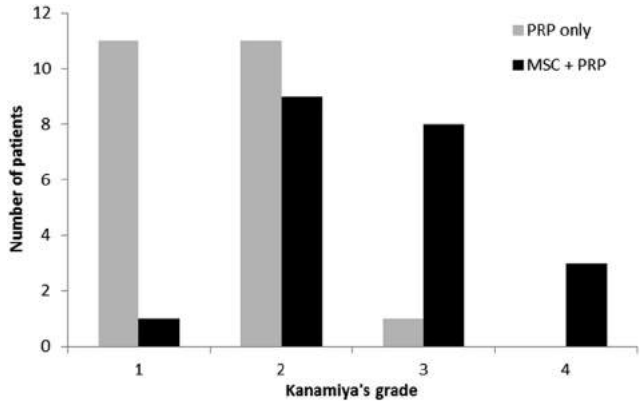

Fig 3. Articular cartilage healing status, using the Kanamiya grading system,[4] during second-look arthroscopy in both groups.

Correlation Between Cartilage Healing Status and Patient Demographic Factors

The correlations between cartilage healing status and other patient demographic factors were analyzed to determine whether there were other reasons for the observed cartilage healing status. However, significant correlations were not found between the cartilage healing status and patient body mass index, age, or radiologic parameters (Table 3).

Discussion

The principal findings of this study were that HTO in conjunction with the use of MSCs plus PRP resulted in good fibrocartilage repair and improved clinical results compared with HTO and PRP only. Importantly, other patient demographic factors, such as age, were not associated with improvements in cartilage healing, suggesting that the improvements were primarily due to MSC injection. Thus these findings support the hypothesis that MSC therapy with PRP, in conjunction with HTO, provided additional benefits for cartilage healing and clinical results compared with injection of PRP only.

HTO has been recommended for treating varus OA to decrease the pressure on the damaged medial compartment of the joint, provide pain relief, and reduce the progression of medial OA.[18] Although HTO theoretically decreases the stress on the load-bearing cartilage in the medial compartment,[2-5] some studies

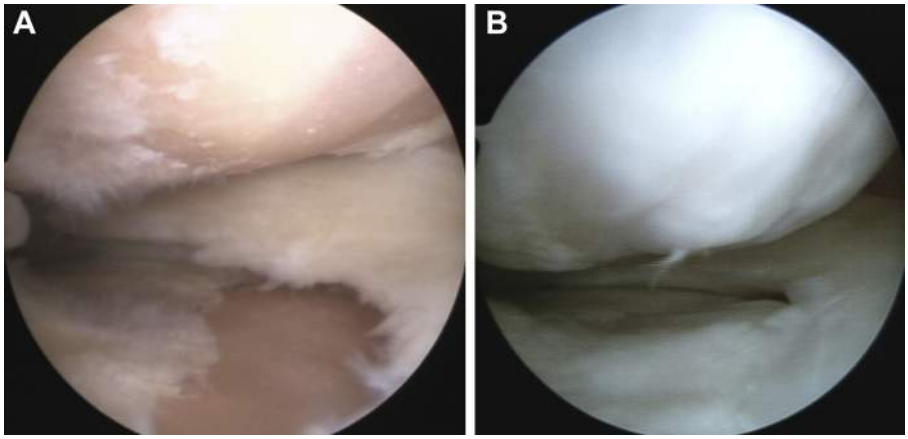

Fig 4. Intraoperative arthroscopic images during first- and second-look arthroscopy. (A) Findings in a 53-year-old woman in the MSC-PRP group. During the first arthroscopy, eburnation of the articular surfaces was found. (B) Marked changes in the cartilage defects of the medial femoral condyle are shown. The articular surface shows an even fibrocartilage coverage at 17 months postoperatively.

have reported that partial remodeling of the articular cartilage occurs with cartilage regeneration after HTO.[19,20] For better chondral defect remodeling, HTO combined with chondral resurfacing has been attempted.[3,21] The most popular chondral resurfacing procedures are marrow stimulation techniques. These techniques involve microfractures that promote cartilage repair by stimulating the bone marrow through the subchondral bone and by producing blood clots containing mesenchymal cells on the articular surface. In a 2-year follow-up study of 38 patients, Sterett and Steadman[21] reported that combining a medial open-wedge HTO with a microfracture in the varus knee was an effective method for decreasing pain and increasing function. However, Mithoefer et al.[22] reported that microfractures effectively improved knee function in all patients during the first 24 months after the microfractures, but the durability of the initial functional improvement was inconsistent. Moreover, in patients with degenerative knee arthritis, the cartilage lesion is diffuse and not focal, meaning that microfractures cannot be applied in all HTO cases. Thus, for cartilage defect remodeling, other options are needed.

MSCs are emerging as powerful tools for cartilage repair because of their ability to differentiate into various connective tissues, including cartilage, bone, and fat.[23,24] The intra-articular injection of MSCs was reported to effectively reduce pain while promoting cartilage regeneration in patients with knee OA.[6,7] On the basis of these previous findings, stem cell injection may be used to achieve greater cartilage remodeling and better clinical results after HTO surgery. Thus, in our study, more patients in the MSC-PRP group achieved partial or even fibrocartilage coverage than in the PRP-only group, showing a clear relation between the cartilage healing status and MSC therapy. Furthermore, the patients in the MSC-PRP group showed statistically significantly better clinical outcomes in the VAS pain score and 2 KOOS subscores compared with patients in the PRP-only group. Although better scores were observed in the group receiving MSC therapy than in the group receiving PRP only, there were no differences between the groups with respect to the Lysholm score and the other KOOS subscores.

Table 3. Correlation Between Cartilage Healing Status and Patient Demographic Factors

	Healing Status	
	Spearman ρ	*P* Value
BMI	0.81	.60
Age	0.09	.56
WBL	0.10	.51
FTA	−0.08	.60

NOTE. Data were calculated using the Spearman rank order correlation test.

BMI, body mass index; WBL, weight-bearing line.

In this study, subcutaneous adipose tissue was used as the stem cell source. Adipose tissue is composed of 2 main cell populations, mature adipocytes and the cells in the SVF. The latter comprise a heterogeneous fraction that includes preadipocytes, endothelial cells, smooth muscle cells, pericytes, macrophages, fibroblasts, and ADSCs, which share several characteristics with bone marrow stem cells.[25,26] ADSCs are promising candidates in a broad range of innovative therapies, ranging from regenerative medicine to tissue engineering. Moreover, the use of ADSCs has been proposed for several chronic diseases, such as Crohn disease,[27] autoimmune pathologies (e.g., multiple sclerosis),[28] and allergic pathologies. The effectiveness against these pathologies can be explained by the immunoregulatory and anti-inflammatory activities of ADSCs and non-expanded SVF cells.[28] Unfortunately, because most studies have focused on in vitro expanded adipose-derived cells, relatively little is known about the potential clinical effects of the whole lipoaspirate, which contains numerous cell populations in addition to MSCs. Recently, ADSCs have been suggested as a new option for the treatment of osteochondral lesions, and the injection of MSCs with marrow stimulation has

been proposed for treating such cases.[29] Moreover, Desando et al.[30] reported that the healing properties of ADSCs, including their promotion of cartilage and meniscus repair and attenuation of inflammatory events in the synovial membrane, may inhibit OA progression. Jurgens et al.[31] evaluated the safety, feasibility, and efficacy of freshly isolated SVF cells and cultured ADSCs in an animal model. They showed the preclinical safety and feasibility of a 1-step surgical procedure for osteochondral defect regeneration using freshly isolated SVF cells and cultured ADSCs. Specifically, they observed similar regeneration induced by either freshly isolated SVF cells or cultured ADSCs.

In OA patients the healing tissue has been shown to be quite different from the surrounding degenerated yellow cartilage. Furthermore, because the cartilage of OA patients has diffuse degenerative lesions, identifying changes in the status of OA patients is difficult. In other words, the grading of severe lesions, used in the Outerbridge classification[32] and the International Cartilage Repair Society grade, does not seem appropriate to describe these changes in the cartilage status of OA patients. Thus the classification of the regenerative progress using the Kanamiya classification,[4] as used in our study, is necessary.

MSC therapy has previously been shown to induce a positive effect in OA treatment through 2 mechanisms, paracrine signaling and end-organ (e.g., cartilage) formation. Paracrine mechanisms likely explain the clinical improvements, whereas cartilage formation explains the differences in cartilage healing status observed between the groups in this study at their final follow-up visit. The MSC therapy method used in this study was a very primitive technique; therefore the method cannot likely be used in isolation. For the application of this technique, several challenges still need to be overcome, including the identification of the optimal sources of stem cells, scaffolds, and growth factors.

Limitations

This study has several limitations. First, the follow-up period was short, and therefore future studies with longer cartilage formation and survival follow-up periods should be undertaken. Second, the stem cells were delivered with a single injection, whereas optimal results may require providing patients with more than 1 injection over time. Third, pathologic examinations of the cartilage properties in each group were not performed. Fourth, the loss of correction influenced the clinical outcome; because patients were not assessed in the standing position, measurement of correction angles in the immediate postoperative period was not performed. Therefore a measure of the influence of correction loss on clinical outcomes was not possible. Fifth, because several patients were excluded because they did not want to undergo plate removal, there might be the problem of selection bias in this study. Sixth, the Kanamiya grading system[4] was a potential limitation because it was not validated with known interobserver and intraobserver variability. Lastly, an additional limitation is the potential for type II errors because of the small sample sizes. Although an a priori power evaluation was conducted to determine the number of participants required for the trial, the calculations were completed using limited data. Therefore the study may suffer from a type II statistical error, resulting from the effects of stem cells on persons with diffuse cartilage lesions. Thus the lack of significant differences in some of the clinical outcome data, with the exception of the pain scores and symptom subscores, was likely because of a type II error. In addition, although statistically significant improvements in some KOOS subscores and in the VAS pain score were observed, they may not reflect clinically significant improvements. Therefore another study will be needed with a larger number of patients.

Conclusions

MSC therapy, in conjunction with HTO, induced mild improvements in cartilage healing and good clinical results in some KOOS subscores and the VAS pain score compared with PRP only.

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