Original Article

Adipose-Derived Stromal Vascular Fractions Are Comparable With Allogenic Human Umbilical Cord Blood–Derived Mesenchymal Stem Cells as a Supplementary Strategy of High Tibial Osteotomy for Varus Knee Osteoarthritis

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Purpose: To compare the clinical, radiologic, and second-look arthroscopic outcomes of high tibial osteotomy (HTO) with stromal vascular fraction (SVF) implantation versus human umbilical cord blood–derived mesenchymal stem cells (hUCB-MSC) transplantation and identify the association between cartilage regeneration and HTO outcomes. **Methods:** Patients treated with HTO for varus knee osteoarthritis between March 2018 and September 2020 were retrospectively identified. In this retrospective study, among 183 patients treated with HTO for varus knee osteoarthritis between March 2018 and September 2020, patients treated with HTO with SVF implantation (SVF group; n = 25) were pair-matched based on sex, age, and lesion size with those who underwent HTO with hUCB-MSC transplantation (hUCB-MSC group; n = 25). Clinical outcomes were evaluated using the International Knee Documentation Committee score and Knee Injury and Osteoarthritis Outcome Score. Radiological outcomes evaluated were the femorotibial angle and posterior tibial slope. All patients were evaluated clinically and radiologically before surgery and during follow-up. The mean final follow-up periods were 27.8 ± 3.6 (range 24-36) in the SVF group and 28.2 ± 4.1 (range, 24-36) in the hUCB-MSC group (P = 0.690). At second-look arthroscopic surgery, cartilage regeneration was evaluated using the International Cartilage Repair Society (ICRS) grade. **Results:** A total of 17 male and 33 female patients with a mean age of 56.2 years (range, 49-67 years) were included. At the time of second-look arthroscopic surgery (mean, 12.6 months; range, 11-15 months in the SVF group and 12.7 months; range, 11-14 months in the hUCB-MSC group, P = .625), the mean International Knee Documentation Committee score and Knee Injury and Osteoarthritis Outcome Score in each group significantly improved (P < .001 for all), and clinical outcomes at final follow-up further improved in both groups when compared with the values at second-look arthroscopic surgery (P < .05 for all). Overall ICRS grades, which significantly correlated with clinical outcomes, were similar between groups with no significant differences (P = .170 for femoral condyle and P = .442 for tibial plateau). Radiologic outcomes at final follow-up showed improved knee joint alignment relative to preoperative conditions but showed no significant correlation with clinical outcomes or ICRS grade in either group (P > .05 for all). **Conclusions:** Improved clinical and radiological outcomes and favorable cartilage regeneration were seen after surgery for varus Knee OA in both SVF and hUCB-MSC groups. **Level of Evidence:** Level III, retrospective comparative study.

Introduction

High tibial osteotomy (HTO) is an established treatment option for patients with medial compartmental knee osteoarthritis (OA) combined with varus malalignment.[1,2] HTO restores joint orientation and axial alignment of the knee by correcting the

medial displacement of the load line and shifting the medial concentration of stress laterally to decrease pressure on the damaged medial compartment.[3-5] However, although HTO can provide an ideal mechanical environment for stopping degenerative changes in articular cartilage by altering the weight-bearing axis, the fundamental long-term success of HTO is controversial if cartilage regeneration of medial OA lesions is not achieved.[6] Although several studies have reported remodeling of the articular cartilage after HTO,[3,7,8] HTO alone induces partial remodeling.[7] Therefore, several authors have suggested the combination of HTO and cartilage repair procedures to obtain adequate regeneration of cartilage in the medial compartment of the knee joint and achieve long-term success of HTO.[3,7,9-12]

Recently, cell-based tissue-engineering approaches have been performed to repair the articular cartilage by filling cartilaginous lesions with mechanically stable hyaline cartilage-like substances that do not deteriorate over time and integrate well with the surrounding tissue.[13] As a potential cell-based therapy for cartilage repair, mesenchymal stem cells (MSCs) have been suggested for treating diseased articular cartilage because of their ability to differentiate into chondrocytes and the paracrine effects of their secreted bioactive materials.[14] The choice of the stem cell source is determined by the ease of harvesting, population density, and differentiation potential of the cells, as these parameters vary across tissues.[15] According to the literature, human umbilical cord blood–derived MSCs (hUCB-MSCs) which can be isolated in a noninvasive manner and are hypoimmunogenic,[16] have shown high expansion capacity, providing sufficient cells for therapeutic applications compared with bone marrow–derived or adipose tissue–derived MSCs.[17] Regarding this, hUCB-MSCs have been used as a supplementary strategy to HTO for better cartilage repair in patients with varus knee OA.[18-20] However, culture expansion is required to obtain a large number of MSCs, which is an expensive and time-consuming procedure that carries risks of contamination.[21] In addition, MSC properties may be altered during culture by various elements of the local microenvironment that can affect differentiation.[22] Conversely, adipose-derived stromal vascular fraction (SVF) has received more attention as an alternative stem cell source for the management of knee OA at any stage, as lipoaspirates are easy to obtain using a minimally invasive procedure with a low complication rate and minimal donor-site morbidity.[23] Adipose-derived SVF cells are a heterogeneous cell population that contains regenerative cells such as adipose-derived MSCs, macrophages, pericytes, fibroblasts, blood cells, and vessel-forming cells including endothelial and smooth muscle cells and their

progenitors.[24] These heterogeneous cell populations include cells with stem cell elements and are thought to have a synergistic effect with adipose-derived MSCs.[25] The purposes of this study were to compare the clinical, radiologic, and second-look arthroscopic outcomes of HTO with SVF implantation versus hUCB-MSC transplantation and identify the association between cartilage regeneration and HTO outcomes. We hypothesized that additional SVF implantation and hUCB-MSC transplantation would be useful in achieving favorable cartilage repair along with better clinical outcomes in patients who underwent HTO.

Methods

Patient Enrollment

The study protocol was approved by the institutional review board of our hospital, and all patients provided written informed consent. Patients treated with HTO for varus knee OA between March 2018 and September 2020 were retrospectively identified. The inclusion criteria were as follows: persistent knee pain not responding to a minimum of 3 months of conservative treatments, grade 3 or 4 OA of the medial compartment on a radiologic assessment according to Kellgren and Lawrence,[26] and the presence of varus malalignment of $\geq 2.5°$ of the knee joint as measured with the femorotibial angle[27] using a full-length, standing radiograph of the entire lower extremity. The exclusion criteria included the following: a history of surgical treatments, grade 3 or 4 OA (Kellgren and Lawrence[26]) lesions of the lateral compartment or patellofemoral compartment, rheumatoid arthritis, hemophilia, post-traumatic OA, active knee infection, chronic anterior cruciate ligament or posterior ligament instability, or mechanical pain caused by meniscal tears. In addition, patients who refused the second-look arthroscopy were excluded in this study.

Study Sample

Between March 2018 and September 2020, a total of 183 patients with medial compartment OA and varus malalignment of the knee joint underwent open-wedge HTO. Among these patients, 27 were excluded and 156 were enrolled in this study. Of the 156 patients, 98 underwent open-wedge HTO with SVF implantation (SVF group), and 58 underwent open-wedge HTO with hUCB-MSC transplantation (hUCB-MSC group). All patients were suggested to undergo second-look arthroscopic surgery after explaining its purpose (to evaluate the medial arthritis lesion and the need for additional arthroscopic procedures such as debridement or synovectomy) before surgery. Of the 98 patients in the SVF group, 12 refused second-look arthroscopic surgery; of the 58 patients in the hUCB-MSC group, 3

refused second-look arthroscopic surgery; 7 and 2 patients in the SVF and hUCB-MSC groups, respectively, were lost to follow-up.

Surgical Procedures

The patients were positioned supine on the operating table and a thigh tourniquet was applied. Before undergoing HTO, all patients underwent arthroscopic procedures including irrigation, synovectomy, debridement, or excision of the degenerative tears of the menisci and removal of articular cartilage fragments, chondral flaps, or osteophytes. SVF was prepared as follows: subcutaneous adipose tissue samples were obtained through tumescent liposuction from the gluteal regions of the patients 1 day before surgery. The aspirated adipose tissue, suspended in phosphate-buffered saline (PBS) solution, was transported to the laboratory and mature adipocytes and connective tissues were separated from the SVF by centrifugation (Hanil Scientific Inc., Gyeonggi-do, Republic of Korea).[26] After washing extensively with PBS, the aspirated adipose tissue was digested at 37°C for 2 hours with 0.1% collagenase and centrifuged at $878 \times g$ for 10 minutes to remove the supernatant. Enzyme activity was neutralized with Dulbecco's modified Eagle's medium, containing 10% fetal bovine serum and centrifuged at $878 \times g$ for 5 minutes to remove impurities. After removal of supernatant, downed SVF pellet was washed with PBS and centrifuged at $562 \times g$ for 5 minutes to remove impurities. The SVF was collected by centrifugation, as detailed previously, filtered through a 100-μm nylon mesh to remove cellular debris. After isolating and characterizing the adipose-derived cells as described previously,[28] we confirmed that the adipose-derived cells contained MSCs. The isolation and characterization procedures determined that adipose-derived stem cells made up 9.5% of the SVF cells. Consequently, an average of 7.6×10^7 SVF cells, which contained an average of 7.2×10^6 stem cells, were used for SVF implantation. Before SVF implantation, arthroscopic debridement of the damaged or undermined cartilage was performed to provide a smooth surface of the cartilage lesion and firm edges facing the surrounding cartilage, and microfracture was performed. The prepared SVFs were loaded into a fibrin glue product, which was used as a scaffold for SVF implantation, from the commercially available Greenplast kit (Green Cross, Seoul, Korea). After the arthroscopic fluid was extracted, the prepared SVFs loaded into the fibrin glue product were implanted into the cartilage lesion site under arthroscopic guidance (Fig 1).

After the arthroscopic procedure, open-wedge HTO was performed as recommended by the AO International Knee Expert Group.[29] The desired correction angle and wedge size was calculated preoperatively using a hip-to-ankle standing anteroposterior (AP) radiograph with the aim of mild overcorrection.[30] 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. This 62.5% of the weight-bearing line ratio, also recognized as the "Fujisawa point," is widely accepted as the target postoperative alignment.[31] Open-wedge HTO was performed with the angular-stable TomoFix plate (Synthes, Solothurn, Switzerland) and the osteotomy site was filled with a β-tricalcium phosphate wedge (Synthes)—a synthetic resorbable substitute having a compressive strength similar to that of cancellous bone—in compliance with the open space. In the hUCB-MSC group, a medicinal product of CARTISTEM (MEDIPOST, Seoul, KR)—a composite of hUCB-MSCs and hyaluronic acid (HA) hydrogel produced according to the regulatory authority and Good Manufacturing Practice guidelines—was used for hUCB-MSC transplantation. This product consists of 1.5 mL of cord blood−derived MSCs (7.5×10^6) and 4% HA. The hUCB-MSCs and HA were mixed according to the manufacturer's instructions before the application during surgery. After performing the HTO, arthrotomy via a medial mini-incision was performed to proceed with the cartilage repair procedures. Multiple drill holes (5 mm in diameter and 5 mm deep) were made approximately 2 to 3 mm apart at the cartilage lesion site of the femoral condyle. In addition, multiple small drill holes (1.4 mm in diameter and 5 mm deep) were made between the 5-mm drill holes for better lateral integration between the repair tissues from the 5-mm drill holes, based on a previous study.[32] The hUCB-MSC and HA hydrogel composite was then implanted into the drill holes in the cartilage lesion site from the base to the surface (Fig 2).[32] One day after surgery, isometric quadriceps, active ankle, and straight leg−raising exercises were started. The patients were allowed to move their knees 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 a radiographic evaluation of bone consolidation at the osteotomy site.

Outcome Assessment

All patients were evaluated clinically and radiologically before surgery and postoperatively at 4 weeks, at 3 months, at 6 months, at 1 year, and at the last follow-up visit (mean 27.8 months; range 24-36 months in the SVF group and mean 28.2 months; range 24-36 months in the hUCB-MSC group, $P = .690$). For the clinical evaluation, the International Knee Documentation Committee (IKDC) score[33,34] and the Knee Injury and Osteoarthritis Outcome
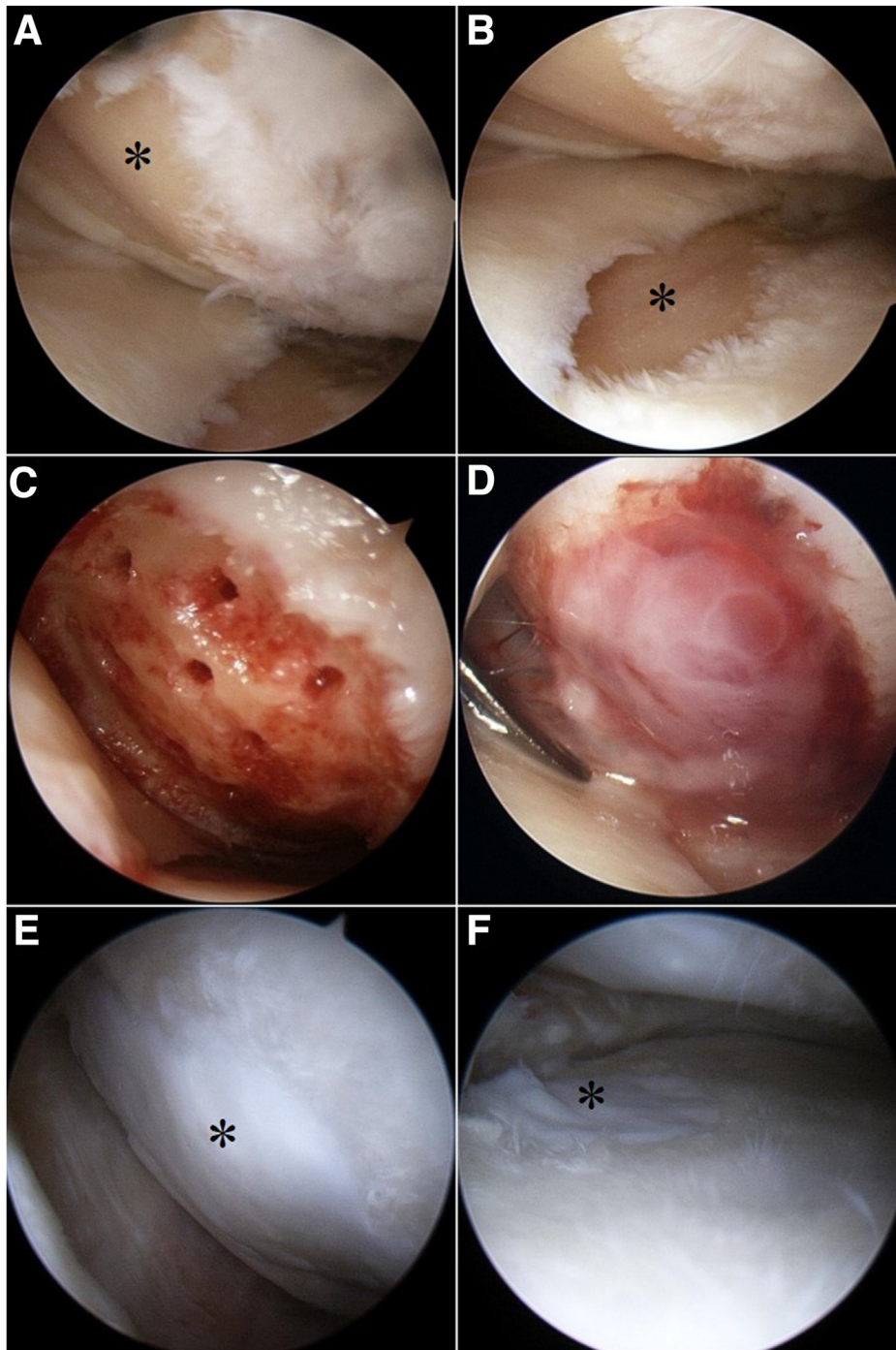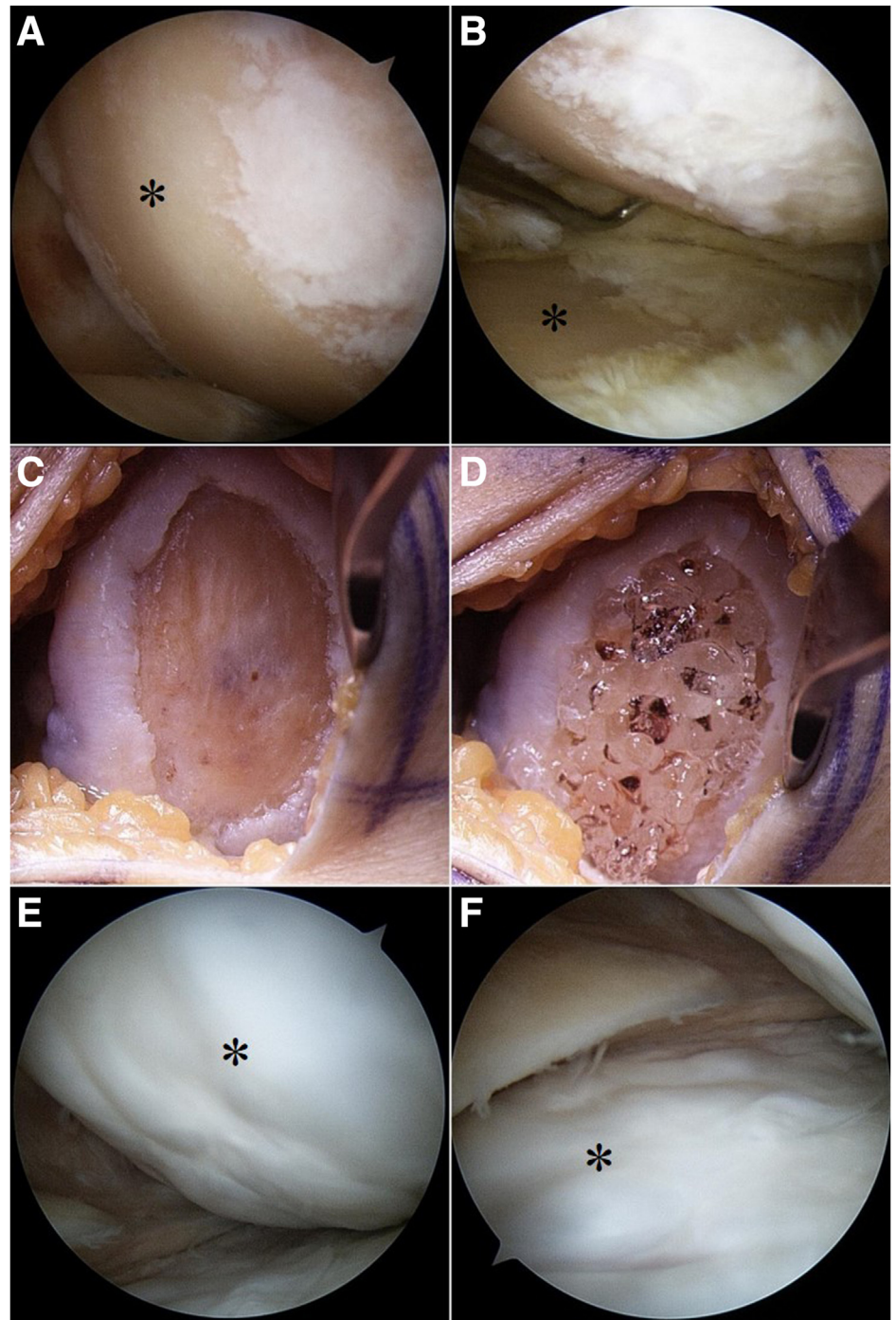
Fig 1. Arthroscopic images of left knee of a 54-year-old woman who underwent high tibial osteotomy with stromal vascular fraction (SVF) implantation. (A, B) Intraoperative arthroscopic view showing articular cartilage lesions in the medial femoral condyle and medial tibial plateau (black asterisks). (C) Microfracture after acute debridement of all unstable and damaged cartilage in the lesion was performed. (D) The cartilage lesion was covered with the SVF–thrombin–fibrinogen suspension. (E, F) Second-look arthroscopic findings showing complete coverage of the lesion site with cartilage (black asterisks).

Score (KOOS)[35,36] were used to determine the joint function and sports activities. Radiographs of the knee joints were obtained, including an AP view, a true lateral view at 30° knee flexion, and an AP long-leg weight-bearing view before surgery. To investigate the mechanical effects of HTO, the femorotibial angle and posterior tibial slope were measured using standing AP radiographs and lateral radiographs, respectively. The femorotibial angle was measured as the angle between the femoral and tibial shaft axes on standing AP radiographs.[27] The posterior tibial slope was measured as the angle formed by the tangent of the medial tibial plateau and the line perpendicular to the tangent at the anterior tibial cortex, with the knee in 30° flexion without rotation of the limb.[37] To avoid potential bias, an independent observer, who was a musculoskeletal-trained radiologist not involved in the care of patients and blinded to the intention of this

Fig 2. Arthroscopic and intraoperative images of left knee of a 52-year-old woman who underwent high tibial osteotomy with human umbilical cord blood−derived mesenchymal stem cell (hUCB-MSC) transplantation. (A, B) Intraoperative arthroscopic view showing articular cartilage lesions in the medial femoral condyle and medial tibial plateau (black asterisks). (C) Cartilage lesion was prepared and debrided down to the bed using curettes until the healthy-looking underlying bone was visible. (D) An hUCB-MSC and hyaluronic acid hydrogel composite was transplanted into the drill holes in the cartilage lesion from the base to the surface. (E, F) Second-look arthroscopic findings showing complete coverage of the lesion site with cartilage (black asterisks).

study, evaluated the radiologic outcomes. Second-look arthroscopic surgery was performed when the plates and screws were removed after radiologic and clinical confirmation of the union of the osteotomy site. During this procedure, cartilage lesions were macroscopically evaluated after arthroscopic marrow simulation using the International Cartilage Repair Society (ICRS)[38] grading system (Table 1). Additional arthroscopic procedures, such as synovectomy, adhesiolysis, or debridement of the impinged soft tissue, were performed if pathologic lesions were found in the knee joints during second-look arthroscopic surgery.

Statistical Analysis

An a priori power analysis based on IKDC revealed that, to obtain a power of 0.80 or greater with a ratio of 1:1, we need a minimum of 25 patients in each group. The primary dependent variables were IKDC score and

Table 1. International Cartilage Repair System (ICRS) Macroscopic Evaluation of Cartilage Repair

Cartilage Repair Assessment (ICRS)	Points
Degree of defect repair	
In level with surrounding cartilage	4
75% repair of defect depth	3
50% repair of defect depth	2
25% repair of defect depth	1
0% repair of defect depth	0
Integration to border zone	
Complete integration with surrounding cartilage	4
Demarcating border <1 mm	3
3/4 of graft integrated, 1/4 with a notable border >1 mm width	2
1/2 of graft integrated with surrounding cartilage, 1/2 with a notable border >1 mm	1
From no contact to 1/4 of graft integrated with surrounding cartilage	0
Macroscopic appearance	
Intact smooth surface	4
Fibrillated surface	3
Small, scattered fissures or cracks	2
Several, small, or few but large fissures	1
Total degeneration of grafted area	0
Overall repair assessment	
Grade I: normal	12
Grade II: nearly normal	11 to 8
Grade III: abnormal	7 to 4
Grade IV: severely abnormal	3 to 1

KOOS at final follow-up as clinical outcomes, postoperative femorotibial angle and posterior tibial slope as radiologic outcomes, and ICRS grade at second-look arthroscopic surgery. The Wilcoxon signed-rank test was performed for the evaluation of changes in preoperative and final follow-up values, while the Mann–Whitney U test was used to compare results between groups. The Fisher exact test was used to compare categorical data. The Spearman rank-order correlation test was used to determine the correlations between the ICRS grade at second-look arthroscopic surgery and clinical outcomes at final follow-up, and the correlations of postoperative radiological outcomes with clinical outcomes at final follow-up and ICRS grades. All analyses were conducted using SPSS, version 13.0 (IBM Corp., Armonk, NY), with statistical significance defined as $P < .05$.

Results

Study Subjects and General Characteristics

After filtering the patients according to the inclusion and exclusion criteria, 79 (SVF group) and 53 (hUCB-MSC group) patients were finally enrolled in this study. From this pool, 50 patients were finally chosen after the matching process (Fig 3). Twenty-five patients treated with open-wedge HTO with SVF implantation were identified and assigned to the SVF group. Twenty-five patients in the hUCB-MSC group were then matched by sex, age, and lesion size to the patients in the SVF group as described to follow. Deidentified patients were individually matched based first on nominal parameters (sex) and then on metric parameters (age and lesion size) by an independent scientist blinded to patient history and clinical complaints. These selected patients were assigned to the hUCB-MSC group. The minimum follow-up time was 24 months for all patients in this study. The final study population included 17 men and 33 women with a mean age of 56.2 (range, 49-67) years. There were no significant differences in body mass index, side of involvement, follow-up period, time to second-look arthroscopy, lesion size, and femorotibial alignment between the groups (Table 2).
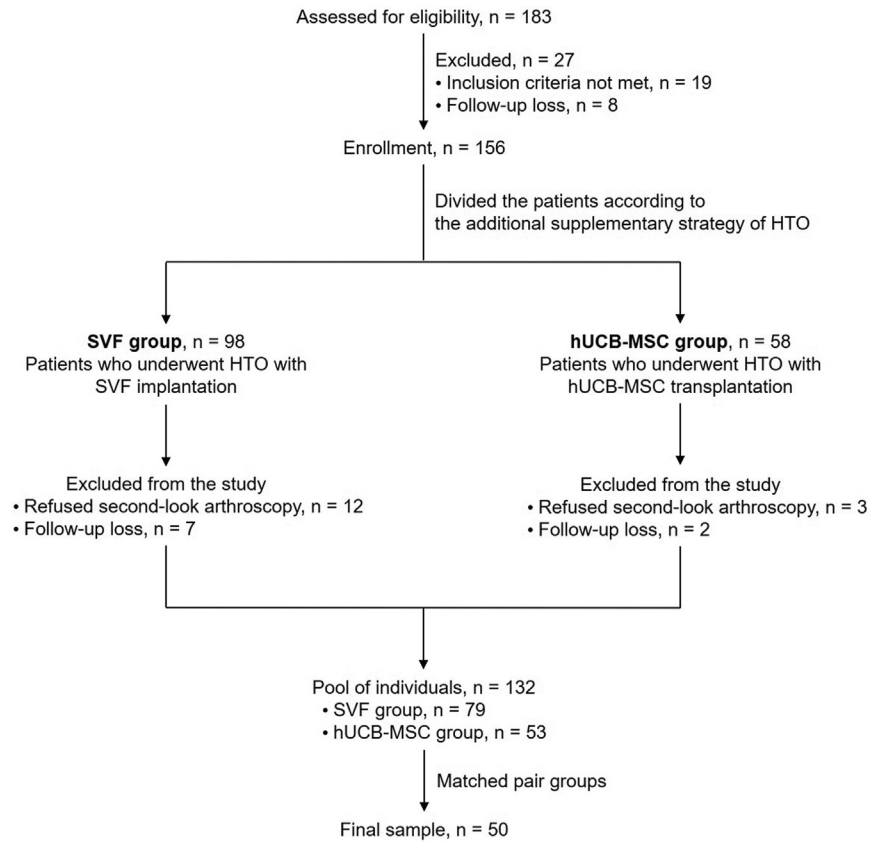
Clinical and Radiologic Outcomes

The clinical outcomes from the preoperative evaluation to the final follow-up for each group are shown in Table 3. The mean IKDC scores and KOOS significantly improved at the time of second-look arthroscopic surgery in both groups ($P < .001$ for all) when compared with preoperative values. At the final follow-up, the mean IKDC scores and KOOS further improved significantly in both groups ($P < .05$ for all), when compared with the values at second-look arthroscopic surgery. During the follow-up, there were no significant differences in the mean IKDC scores and KOOS between groups ($P > .05$ for all). Radiologic outcomes at the final follow-up showed a corrected knee joint alignment compared with the preoperative states. The mean femorotibial angle and posterior tibial slope changed significantly from varus $3.4 \pm 0.6°$ and $10.3 \pm 0.9°$ to valgus $8.8 \pm 0.3°$ and $10.3 \pm 0.8°$ ($P < .001$ for both), respectively, in the SVF group and from varus $3.3 \pm 0.5°$ and $10.1 \pm 0.7°$ to valgus $8.8 \pm 0.3°$ and $10.3 \pm 0.8°$ ($P < .001$ for both), respectively, in the hUCB-MSC group (Table 4). However, there were no significant differences in the mean femorotibial angle and posterior tibial slope between the groups (Table 4).

Second-Look Arthroscopic Outcomes

Second-look arthroscopic surgery was performed before the removal of plates and screws at a mean of 12.6 months postoperatively (range, 11-15 months) in the SVF group and a mean of 12.7 months postoperatively (range, 11-14 months) in the hUCB-MSC group ($P = .625$). The ICRS grades of each group are summarized in Table 5. According to the ICRS grades, 44% and 64% of lesions in the SVF and hUCB-MSC groups, respectively, were grade I or II on the femoral condyle. Similarly, 52% and 64% of lesions in the SVF and hUCB-MSC groups, respectively, were grade I or II on the tibial plateau. The overall ICRS grades were relatively better in the hUCB-MSC group than in the SVF group. However, there were no significant differences in ICRS grades between the groups

Fig 3. Flow diagram of patient recruitment in the study. (HTO, high tibial osteotomy; hUCB-MSC, human umbilical cord blood−derived mesenchymal stem cell; SVF, stromal vascular fraction.)

regarding the femoral condyle ($P = .170$) and tibial plateau ($P = .442$).

Correlations Between Clinical, Radiologic, and Second-Look Arthroscopic Outcomes

At second-look arthroscopic surgery, ICRS grades significantly correlated with clinical outcomes in both groups ($P < .05$ for all) (Table 6). In other words, as the quality of repaired cartilage increased, the IKDC scores and KOOS increased significantly in both groups. However, postoperative radiologic outcomes were not correlated with clinical outcomes at the final follow-up or ICRS grades at the time of second-look arthroscopic surgery (Table 7).

Table 2. Patient Demographic Characteristics in Both Groups

	SVF (n = 25)	hUCB-MSC (n = 25)	P Value
Age, y	56.0 ± 4.8 (range, 49-65)	56.4 ± 6.0 (range, 49-67)	.816
Sex, male/female, n	8/17	9/16	.771
Body mass index	26.1 ± 2.9 (range, 19.6-32.5)	26.5 ± 2.7 (range, 23.0-32.5)	.602
Side of involvement, right/left, n	12/13	14/11	.580
Follow-up period, mo	27.8 ± 3.6 (range 24-36)	28.2 ± 4.1 (range, 24-36)	.690
Time to second-look arthroscopy, mo	12.6 ± 0.9 (range, 11-15)	12.7 ± 0.9 (range, 11-14)	.625
Lesion size, cm^2			
Femoral condyle	5.5 ± 1.8 (range, 2.6-8.9)	5.7 ± 1.9 (range, 2.7-9.5)	.731
Tibial plateau	4.5 ± 1.4 (range, 3.0-7.8)	4.5 ± 1.6 (range, 2.3-8.7)	.883
Femorotibial angle (varus), deg	3.4 ± 0.6 (range, 2.8-5.3)	3.3 ± 0.5 (range, 2.8-5.0)	.614
Posterior tibial slope, deg	8.8 ± 0.3 (range, 8.5-9.6)	8.8 ± 0.3 (range, 8.1-9.3)	.722

NOTE. Data are presented as mean ± standard deviation (range) unless otherwise indicated.

hUCB-MSC, human umbilical cord blood−derived mesenchymal stem cell; SVF, stromal vascular fraction.

Table 3. Comparison of Serial Clinical Outcomes in Both Groups

	SVF (n =25)	hUCB-MSC (n =25)	P Value*
IKDC score			
Preoperative	38.5 ± 4.1	37.9 ± 4.3	.578
Second-look arthroscopy	67.4 ± 6.2	67.0 ± 6.3	.800
Final follow-up	72.4 ± 6.1	71.8 ± 6.1	.793
P value†	<.001	<.001	
P value‡	<.001	<.001	
KOOS Pain			
Preoperative	42.4 ± 5.3	42.0 ± 6.1	.846
Second-look arthroscopy	73.6 ± 5.8	72.6 ± 5.3	.397
Final follow-up	79.5 ± 5.7	78.7 ± 5.7	.560
P value†	<.001	<.001	
P value‡	<.001	<.001	
KOOS Symptom			
Preoperative	41.2 ± 5.2	42.9 ± 5.8	.930
Second-look arthroscopy	78.1 ± 5.6	77.6 ± 5.4	.748
Final follow-up	81.2 ± 6.4	79.3 ± 5.7	.173
P value†	<.001	<.001	
P value‡	<.001	.009	
KOOS Activities of Daily Living			
Preoperative	52.2 ± 6.2	52.3 ± 5.3	.977
Second-look arthroscopy	79.9 ± 5.7	78.5 ± 5.8	.268
Final follow-up	83.6 ± 5.8	83.9 ± 5.4	.838
P value†	<.001	<.001	
P value‡	<.001	<.001	
KOOS Sports and Recreation			
Preoperative	23.3 ± 4.5	23.2 ± 4.6	.915
Second-look arthroscopy	62.4 ± 4.0	62.0 ± 4.8	.748
Final follow-up	64.4 ± 4.9	64.0 ± 5.2	.838
P value†	<.001	<.001	
P value‡	.002	.001	
KOOS Quality of Life			
Preoperative	31.4 ± 6.6	31.1 ± 6.0	.756
Second-look arthroscopy	68.6 ± 6.2	67.8 ± 6.9	.613
Final follow-up	73.7 ± 6.0	72.6 ± 6.0	.409
P value†	<.001	<.001	
P value‡	<.001	<.001	

NOTE. Data are presented as mean ± standard deviation.

hUCB-MSC, human umbilical cord blood–derived mesenchymal stem cell; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; SVF, stromal vascular fraction.

*Mann–Whitney U test.

†Wilcoxon signed-rank test for comparison of clinical outcomes at second-look arthroscopy versus preoperative values.

‡Wilcoxon signed-rank test for comparison of clinical outcomes at second-look arthroscopy versus final follow-up.

Discussion

The principal findings of the present study are that the clinical and radiologic outcomes (the femorotibial angle and posterior tibial slope) significantly improved after surgery in both groups, and although the overall ICRS grades at second-look arthroscopy were relatively better in the hUCB-MSC group than in the SVF group, there were no significant differences in ICRS grades between groups. Moreover, cartilage regeneration according to ICRS grade was significantly correlated with clinical outcomes in both groups. In addition, the clinical outcomes were further improved from the time of second-look arthroscopic surgery to the final follow-up in both groups. In contrast, postoperative radiologic outcomes were not significantly correlated with clinical outcomes or ICRS grades. Therefore, improved cartilage regeneration may be attributed to better clinical outcomes regardless of which treatment was administered.

In patients with varus knee OA, the increased joint load concentrated on the medial compartment of the knee joint causes continuous degeneration of the cartilage, which leads to the progression and worsening of medial compartment knee OA. Therefore, ideal treatments for varus knee OA should restore the crucial biochemical and biomechanical properties of the degenerated cartilage.[39] Adequate knee joint orientation and axial alignment can be achieved by performing HTO in patients with varus knee OA, and the biomechanical environment that is essential for cartilage regeneration can be provided by performing HTO. However, although partial remodeling of the articular cartilage can be achieved after HTO,[3,7,8] the recovery of the biochemical properties of the degenerated cartilage is insufficient with HTO alone and the articular surface may continue to degrade and lead to exacerbation of knee OA despite performing HTO. Thus, several authors have performed cartilage repair procedures as a supplementary to concomitant HTO to provide the biochemical environment, as well as the biomechanical environment, for cartilage regeneration in the medial compartment of the knee joint.[1,3,7,9-12,18,40] This viewpoint is also supported by several studies that have reported a positive correlation between cartilage regeneration and clinical outcomes of HTO.[11,41,42]

Recently, cell-based therapies have emerged as a potential therapeutic option for the management of knee OA.[43] Regarding this, MSCs from various sources have been extensively evaluated for their ability to restore compromised articular cartilage and slow the progression of knee OA.[44] Since the pathogenesis of OA is based on degeneration and inflammation, the therapeutic properties of MSCs, including paracrine,[14,45] anti-inflammatory,[46] and immunomodulatory effects,[47] can help restore the intra-articular environment.[48] Therefore, MSCs also can be applied in patients with varus knee OA to achieve greater cartilage regeneration, and, subsequently, better clinical outcomes after HTO. From this viewpoint, several authors have suggested the application of MSCs to achieve superior cartilage regeneration accompanied by more favorable clinical outcomes in patients who undergo HTO.[1,18,20,40,41,49] According to the literature, hUCB-MSCs have various advantages compared with MSCs from other sources as follows. The hUCB-MSCs are relatively easy to collect and have a similar expansion capacity to that of bone marrow- or adipose-derived

Table 4. Comparison of Serial Radiologic Outcomes in Both Groups

	SVF (n = 25)	hUCB-MSC (n = 25)	P Value*
Femorotibial angle, °			
Preoperative (varus)	3.4 ± 0.6 (range, 2.8-5.3)	3.3 ± 0.5 (range, 2.8-5.0)	.592
Final follow-up (valgus)	8.8 ± 0.3 (range, 8.5-9.6)	8.8 ± 0.3 (range, 8.1-9.3)	.937
P value†	<.001	<.001	
Posterior tibial slope, °			
Preoperative	10.3 ± 0.9 (range, 8.9-11.8)	10.1 ± 0.7 (range, 8.6-11.6)	.460
Final follow-up	10.3 ± 0.8 (range, 8.6-11.9)	10.3 ± 0.8 (range, 8.8-12.1)	.876
P value†	<.001	<.001	

NOTE. Data are presented as mean ± standard deviation (range).

hUCB-MSC, human umbilical cord blood−derived mesenchymal stem cell; SVF, stromal vascular fraction.

*Mann−Whitney *U* test.

†Wilcoxon signed-rank test for comparison of clinical outcomes at final follow-up versus preoperative values.

MSCs.[17,44] They cause less donor-site morbidity and have a greater proliferation rate and chondrogenic potential than bone marrow−derived MSCs.[50] For these reasons, several previous studies suggested the application of hUCB-MSCs for the treatment of knee OA,[32,51,52] and several authors reported the use of hUCB-MSCs in patients with varus knee OA who underwent concomitant HTO.[18,19,53] Suh et al.[19] evaluated the clinical and radiologic outcomes of patients who had undergone hUCB-MSC treatment combined with HTO (hUCB-MSC group) and compared them with those of patients who had undergone microfracture combined with HTO (control group). They reported a mean postoperative IKDC score of 84.0 ± 11.2 in the hUCB-MSC group and 79.2 ± 13.0 in the control group; this difference was significant (*P* = .002). They also found a statistically significant difference in the joint space width increment between the 2 groups (0.6 mm in the hUCB-MSC group, 0.1 mm in the control group; *P* = .036). Yang et al.[53] evaluated a total of 176 patients who underwent HTO combined with a bone marrow aspirate concentrate (BMAC) or hUCB-MSC procedure for medial compartment knee OA and compared the clinical and second-look arthroscopic outcomes between the groups. They found that at a mean follow-up of 33 months, clinical outcomes

including IKDC, KOOS, Short-Form 36, and Tegner activity scores were significantly improved in both groups (*P* < .001); however, there were no differences between the groups. They also reported that second-look arthroscopy showed better healing of regenerated cartilage in the hUCB-MSC group than in the BMAC group according to the ICRS grading system (*P* = .040). Moreover, ICRS grades at second-look arthroscopy were significantly correlated with clinical outcomes (r = −0.337; *P* = .002). They concluded that both treatments provided similar, reliable outcomes in terms of pain relief, functional scores, and quality of life at a mean follow-up of 33 months. However, hUCB-MSC implantation was more effective than BMAC augmentation for articular cartilage regeneration. Lee et al.[18] compared the outcome of cartilage regeneration between 42 cases of BMAC augmentation (BMAC group) and 32 cases of hUCB-MSCs transplantation (hUCB-MSC group) in 74 patients who underwent HTO for varus knee OA. They reported that the clinical outcomes in both groups improved with no significant differences, and the ICRS grade at second-look arthroscopy was significantly better in the hUCB-MSC group than in the BMAC group in both medial femoral and medial tibial cartilage (*P* = .001 for both). Similar to the aforementioned studies, the clinical outcomes in the present study were significantly improved regardless of which treatment was administered. In addition, ICRS grades at second-look arthroscopic surgery significantly correlated with clinical outcomes at the time of second-look arthroscopic surgery in both groups (*P* < .05 for all) (Table 6). Therefore, we believe that the correction of varus malalignment of the knee can stimulate remodeling of the articular cartilage and ameliorate the destructive processes,[3,7,8] and subsequently, improve the clinical outcomes at the time of second-look arthroscopic surgery in both groups (Tables 3 and 4). Moreover, considering that further improvement of the clinical outcomes at final follow-up was observed in both groups (Table 3), we believe that remodeling of the

Table 5. ICRS Grades at Second-Look Arthroscopy According to the Location of Cartilage Lesions in Both Groups

	Femoral Condyle			Tibial Plateau		
	SVF Group	hUCB-MSC Group	*P* Value	SVF Group	hUCB-MSC Group	*P* Value
ICRS grade			.170			.443
I	3 (12)	5 (20)		4 (16)	6 (24)	
II	8 (32)	11 (44)		9 (36)	10 (40)	
III	9 (36)	6 (24)		8 (32)	7 (28)	
IV	5 (20)	3 (12)		3 (2)	2 (8)	

NOTE. Data are presented as number (%).

hUCB-MSC, human umbilical cord blood−derived mesenchymal stem cell; ICRS, International Cartilage Repair Society; SVF, stromal vascular fraction.

Table 6. Correlations Between ICRS Repair Grades at Second-Look Arthroscopy and Clinical Outcomes at the Time of Second-Look Arthroscopy in Both Groups

	ICRS Repair Grade							
	Femoral Condyle				Tibial Plateau			
	SVF		hUCB-MSC		SVF		hUCB-MSC	
	S rho	P	S rho	P	S rho	P	S rho	P
IKDC score	−0.495	.012	−0.705	<.001	−0.510	.009	−0.667	<.001
KOOS								
Pain	−0.592	.002	−0.831	<.001	−0.657	<.001	−0.789	<.001
Symptom	−0.618	.001	−0.828	<.001	−0.658	< .001	−0.773	.023
Activities of Daily Living	−0.526	.007	−0.803	<.001	−0.551	.004	−0.770	<.001
Sports and Recreation	−0.785	<.001	−0.617	.001	−0.831	< .001	−0.590	.002
Quality of Life	−0.728	<.001	−0.834	<.001	−0.748	< .001	−0.784	<.001

NOTE. Data are calculated using the Spearman rank-order test.

hUCB-MSC, human umbilical cord blood-derived mesenchymal stem cell; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; S, Spearman; SVF, stromal vascular fraction.

articular cartilage by the correction of varus malalignment contributed to the improved clinical outcomes at second-look arthroscopic surgery, and the further improvement observed in both groups might be a result of the greater durability of repaired cartilage with an SVF implantation or hUCB-MSC transplantation, which provided better cell survival, proliferation, differentiation, and matrix synthesis associated with greater initial mechanical integrity. In addition, as we were concerned that the radiologic outcomes might confound the association between cartilage regeneration and the outcomes of HTO, we analyzed the correlations between corrected knee alignment and the clinical outcomes in both groups. However, no radiologic outcomes had a significant influence on the clinical outcomes or ICRS grade (Table 7). Therefore, we believe that both supplementary strategies (SVF implantation and hUCB-MSC transplantation) of HTO were effective treatment options for the treatment of

varus knee OA that could provide the biomechanical and biochemical environment for cartilage regeneration.

In previous studies that compared the outcome of cartilage regeneration between BMAC augmentation and hUCB-MSCs transplantation as supplementary strategies of HTO for the treatment of varus knee OA, ICRS grades at second-look arthroscopy were significantly better in patients treated with hUCB-MSCs transplantation than in those who underwent BMAC augmentation.[18,53] However, in the present study, although the overall ICRS grades at second-look arthroscopy were relatively better in the hUCB-MSC group than in the SVF group, there were no significant differences in ICRS grades between groups. Although we cannot explain the exact reason why there were no significant differences between groups, we speculate the reasons as follow. First, the number of MSCs applied in the present study was similar in both

Table 7. Correlations Between Postoperative Radiologic Outcomes and Clinical Outcomes at Final Follow-up and ICRS Grades at Second-Look Arthroscopy in Both Groups

	Femorotibial Angle				Posterior Tibial Slope			
	SVF		hUCB-MSC		SVF		hUCB-MSC	
	S rho	P	S rho	P	S rho	P	S rho	P
IKDC score	0.224	.281	0.293	.148	0.225	.294	0.273	.254
KOOS								
Pain	0.241	.371	0.231	.187	0.264	.372	0.164	.376
Symptom	0.253	.264	0.153	.364	0.276	.310	0.327	.089
Activities of Daily Living	0.378	.079	0.128	.479	0.354	.084	0.128	.513
Sports and Recreation	0.323	.116	0.179	.317	0.308	.143	0.138	.452
Quality of Life	0.392	.152	0.294	.214	0.326	.178	0.278	.264
ICRS grades								
Femoral condyle	−0.156	.458	−0.178	.361	−0.143	.143	−0.218	.112
Tibial plateau	−0.125	.550	−0.137	.487	−0.238	.179	−0.279	.094

NOTE. Data are calculated using the Spearman rank-order test.

hUCB-MSC, human umbilical cord blood−derived mesenchymal stem cell; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; S, Spearman; SVF, stromal vascular fraction.

groups. In the SVF group, an average of 7.6×10^7 SVF cells, which contained an average of 7.2×10^6 stem cells, were used for SVF implantation, and a medicinal product of CARTISTEM (MEDIPOST, Seoul, KR) consisting of cord blood−derived MSCs (7.5×10^6) and 4% HA was used for hUCB-MSC transplantation in the hUCB-MSC group. In previous studies that compared the outcome of cartilage regeneration between BMAC augmentation and hUCB-MSCs transplantation as supplementary strategies of HTO for the treatment of varus knee OA,[18,53] the number of MSCs in BMAC was smaller than the number of MSCs in SVF in the present study. This is because it is known that only approximately 0.001% of nucleated cells from BMAC are MSCs.[54] Second, we believe that the fibrin glue used as a scaffold in the SVF group played a role in effective cartilage regeneration. Because the scaffold provides sufficient functional properties at the time of implantation, seeding MSCs in scaffolds can provide initial mechanical integrity for resurfacing the joint with a biologic implant. The scaffold should be conducive to cell attachment and migration, permitting appropriate extracellular matrix formation and the transmission of signaling molecules.[55,56] Fibrin, a tissue-derived natural material that can be used as a 3-dimensional scaffold, is a protein involved in the clotting of blood, and it is formed by the polymerization of fibrin glue in the presence of thrombin. Fibrin glue promotes the proliferation and gene expression of MSCs.[57] Therefore, fibrin glue has been used widely during the development of articular cartilage repair strategies as a cell delivery matrix for generating new cartilage matrices.[58,59] Development of an advanced cell-based tissue engineering approach using MSCs for cartilage regeneration should possess the ability to repair with a mechanically stable cartilage-like substance, resistance to deterioration over time, and sufficient integration with the surrounding tissue. We believe that SVF loaded into the fibrin glue product, which was implanted into the cartilage lesion site, meets these requirements and consequently favorable cartilage regeneration was achieved after SVF implantation. Lastly, SVF is composed of a heterogeneous cell population that contributed to effective cartilage regeneration. Unlike cultured adipose-derived MSCs, which constitute a fairly homogenous cell population, SVF is a heterogeneous cell population containing regenerative cells, such as adipose-derived MSCs, macrophages, pericytes, fibroblasts, blood cells, and vessel-forming cells and their progenitors.[24] SVF is a promising candidate for the regenerative treatment of OA because it contains a significant proportion of cells involved in immunoregulation[60] and a variety of regenerative cells that may act synergistically with adipose-derived MSCs.[61,62] Adipose-derived stem and stromal cells contribute to cartilage regeneration by tissue-specific differentiation, extracellular matrix secretion, and various immune-modulating factor secretions.[63,64] In addition, macrophages, which constitute 20% of SVF cells, are known to be involved in anti-inflammatory activities.[65] Fibroblasts secrete extracellular matrix components that positively influence cell adhesion, migration, and cell-matrix interactions.[66] Regarding these reasons, we think that no significant differences were found in ICRS grades between the groups, which indicated that SVF implantation could obtain cartilage regeneration as favorable as hUCB-MSC transplantation. Therefore, considering that a medicinal product of CARTISTEM (MEDIPOST) used for hUCB-MSC transplantation is an allogenic product, costs more than SVF implantation, and requires open arthrotomy that results in late recovery, we suggest SVF implantation as a supplementary strategy of HTO for better cartilage regeneration in patients with varus knee OA.

Limitations

The present study has several limitations. First, the number of patients was relatively small, and the data were collected retrospectively. However, matching according to sex, age, and lesion size in combination with the strict inclusion and exclusion criteria resulted in a homogeneous distribution of all parameters that could have potentially influenced postoperative outcomes. Therefore, we believe that these data are valuable for comparison of the outcomes of SVF implantation and hUCB-MSC transplantation as supplementary strategies of HTO in patients with varus knee OA. Second, we used the IKDC score and KOOS to evaluate clinical outcomes and ICRS grades to investigate second-look arthroscopic outcomes after surgery. It is important to examine the mechanical properties and biological functions of the regenerated cartilage and compare them with those of native cartilage. Although a biopsy with a histologic evaluation is the most reliable method to examine the biomechanical properties of regenerated cartilage, we could not conduct biopsies solely for research purposes because of ethical issues related to possible morbidity. Third, second-look arthroscopic surgery was performed 1 year postoperatively. It is unknown how the repaired cartilage behaves over the long term, and changes in the influential factors after the first postoperative year cannot be predicted at present. Fourth, the optimal number of MSCs to be applied remains unknown. In this study, an average of 7.6×10^7 SVF cells, which contained an average of 7.2×10^6 stem cells, were used for SVF implantation, and 7.5×10^6 cord blood−derived MSCs were used for hUCB-MSC transplantation. The lesion sizes in the present study were relatively small in both groups compared with those in the previous studies.[18,64] Thus, favorable cartilage regeneration might be achieved by the given

number of MSCs used in both groups. Surely, a larger number of MSCs will be required to obtain an adequate extent of repair for larger-sized lesions. Further studies are required to determine the optimal number of MSCs required for better clinical outcomes and articular cartilage regeneration. Lastly, the SVF implantation was performed arthroscopically and the hUCB-MSC transplantation was performed with arthrotomy. The difference of procedure methods might affect the outcomes. Therefore, more precise evaluation considering the role of procedure methods is required in future studies.

Conclusions

Improved clinical and radiologic outcomes and favorable cartilage regeneration were seen after surgery for varus knee OA in both SVF and hUCB-MSC groups.

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