Original Article

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High tibial osteotomy with cartilage regeneration surgery using human umbilical cord blood-derived mesenchymal stem cells for medial compartment osteoarthritis of the knee

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Background: To compare clinical and radiological outcomes in high tibial osteotomy (HTO) with or without cartilage regeneration surgery using human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) for medial compartment osteoarthritis of the knee.
Methods: Patients who underwent HTO only (group H) or HTO with cartilage regeneration surgery using hUCB-MSCs (group HS) were retrospectively reviewed, and these patients had a minimum radiographic and clinical follow-up period of 12 months. The following radiologic parameters were evaluated: hip-knee-ankle angle, tibia plateau inclination, knee joint line orientation, ankle joint line orientation, medial and lateral joint width, and joint line convergence angle. Moreover, the clinical score was evaluated according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and International Knee Documentation Committee (IKDC) scores.
Results: A total of 44 knees (group H: 32, group HS: 12) were enrolled. The mean age of group H and group HS were 57.2 and 55.1 respectively. No significant difference in preoperative radiologic parameters and clinical outcomes was observed between the two groups (all $P > 0.05$). Significant improvements were observed between pre- and postoperative radiologic parameters, except for medial joint width, in both groups. However, these parameters were not significantly different in both groups (all $P > 0.05$). At the last follow-up, significant improvements were observed in WOMAC and IKDC scores compared with the preoperative score in both groups. However, no differences were observed between the two groups (all $P > 0.05$).
Conclusion: Satisfactory clinical and radiological outcomes were observed in both groups in short-term follow-up. However, no significant difference in clinical and radiological outcomes was observed between the two groups at the last follow-up moment. In the future, a study with medium- to long-term follow-up is needed.

Keywords: Osteotomy; Stem cell; Human umbilical cord blood-derived mesenchymal stem cell; Knee osteoarthritis; Cartilage

INTRODUCTION

High tibial osteotomy (HTO) is an established procedure for the treatment of young and active patients with medial compartment osteoarthritis (OA) by changing the alignment of the lower limb [1,2]. Several surgeons have reported that HTO was effective in pain relief and caused significant changes in radiologic parameters and showed good long-term results. Furthermore, several studies have reported remodeling of the articular cartilage after HTO and attributed improvement to reduced contact stress [3–5]. However, HTO alone can induce only partial remodeling of the articular cartilage [5]. HTO is a joint-preserving procedure; therefore, healthy articular cartilage is critical for good results. Consequently, medial femoral condylar cartilage wear is a challenging issue when per-

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forming an HTO procedure.

Several surgeons have reported that HTO with cartilage regeneration surgery shows significant pain relief and functional restoration; there are several additional treatment options concomitant with HTO for medial femoral condylar cartilage lesions for cartilage regeneration, including injection or implantation of platelet-rich plasma (PRP) [6], bone marrow aspirate concentrate (BMAC), and human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) [6–8]. hUCB-MSCs are allogenic mesenchymal stem cells and progenitor cells attained from human umbilical cord blood. hUCB-MSCs have an additional advantage owing to their high expansion capacity, noninvasive harvesting, and hypo-immunogenicity. Moreover, because they are allogenic stem cells, surgeons can supply a sufficient amount of stem cells.

However, there are few studies investigating the effect of additional cartilage regeneration surgery concomitant with HTO on radiologic parameters and clinical outcomes compared with HTO only. This study aimed to compare clinical outcomes and radiologic parameters in HTO only versus HTO with cartilage regeneration surgery using hUCB-MSCs. We hypothesized that cartilage regeneration surgery would cause differences in radiologic parameters and significant improvement in clinical outcomes compared with the control group.

METHODS

Patient enrollment

A retrospective review of patients who underwent medial open wedge HTO from January 2015 to November 2019 was conducted. Patients (1) with medial compartment OA (2) who underwent HTO only (group H) or HTO with cartilage regeneration surgery using hUCB-MSCs (group HS) were included. Patients who underwent surgery owing to other diseases other than primary OA and those with a follow-up period of < 12 months were excluded (Fig. 1). All patients were informed regarding the purpose, procedure of HTO, and benefit of additional cartilage regeneration surgery. Subsequently, patients voluntarily decided whether to undergo cartilage regeneration surgery concomitant with HTO or not. This study was approved by the Institutional Review Board of Board of Keimyung University Dongsan Hospital (No. 2021-04-075) and written inforemd consent was obtained from all patients.

Surgical methods and postoperative management

Preoperatively, correction angle and height were measured using the Miniaci technique to correct the mechani-

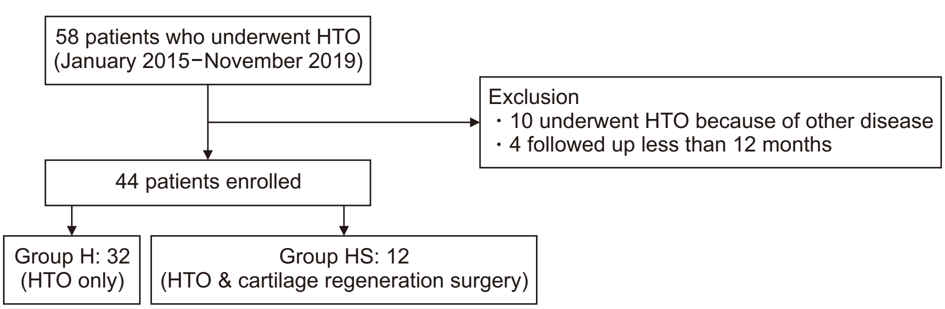

Fig. 1. Patients' enrollment flowchart. HTO, high tibial osteotomy.

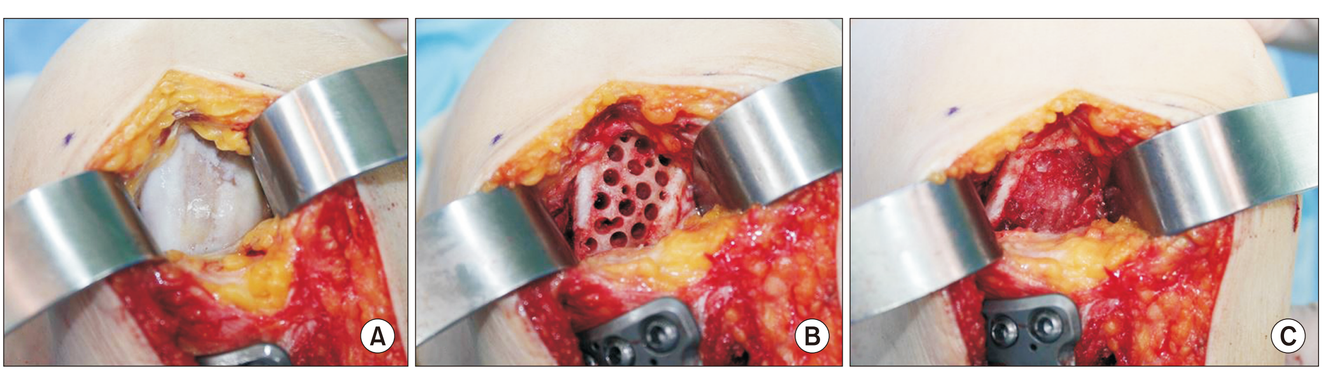

Fig. 2. Arthrotomy was performed and exposed the medial condyle of the femur after high tibial osteotomy (HTO). (A) Debridement, (B) creating multiple holes, and (C) stem cell implantation were performed.

cal axis to pass the Fujisawa point [9,10]. For the surgical procedure, arthroscopy was performed for the first time in all patients who underwent HTO. During arthroscopy, the medial femoral condylar cartilage defect size was examined. Medial open wedge HTO was subsequently performed. A proximal anteromedial incision was made, and the pes anserinus was identified. Preserving the pes anserinus, biplanar medial open wedge osteotomy was performed. After widening the osteotomy site, the gap was measured; using a prepared hydroxyapatite block (Otho biowedge; Ohtomedical Co. Ltd., Goyang, Korea), the gap of the open wedge osteotomy site was filled. Finally, the plate (Ohtofix; Ohtomedical Co. Ltd.) was fixed using cortical and locking screw. In group HS, arthrotomy was performed, and the medial condyle of the femur was exposed after HTO. The cartilage defect was examined, and the defect size was measured again. After debridement and creating multiple holes, we implanted 3 mL (2 vials) of hUCB-MSCs (CARTISTEM®; Medipost, Seongnam, Korea) with hyaluronic acid (Fig. 2). It consisted of 7.5 × 10^6 allogenic umbilical cord blood-derived mesenchymal stem cells per vial.

Postoperatively, we took a cylinder splint for 3 days with full knee extension state and educated patients to avoid weight bearing on the operated limb for 6 weeks. Three days postoperatively, we did not limit continuous passive motion exercise of the knee. Six weeks postoperatively, we started protected weight bearing with crutch and informed patients to ambulate gradually.

Radiologic parameters

To assess intra- and interobserver reliabilities, two orthopedic surgeons respectively evaluated preoperative, postoperative 6 months, 1 year, and the latest radiologic parameters twice 3 months after the first evaluation. Intraclass correlation coefficients were used to determine intra- and interobserver reliabilities, and both showed good to excellent (range, 0.91–0.99).

Hip-knee-ankle angle (HKA) was evaluated as the angle between the mechanical axis of the femur and the mechanical axis of the tibia (Fig. 3A) [3]. Tibia plateau inclination (TPI) was defined as (the angle between the mechanical axis of the tibia and the tangent to the subchondral plate of the proximal tibia) –90°; TPI shows negative values in the varus alignment (Fig. 3B) [3]. Ankle joint line orientation (AJLO) was defined as the angle between the tangent to the subchondral plate of the talus and the horizontal grid line on radiographs; a negative value was given when the tangent of the talus surface tilted medially relative to the horizontal grid line. Lateral tilting was defined as a positive value and medial tilting as a negative value (Fig. 3C) [3].

On the knee standing AP radiograph, medial and lateral joint widths (MJW and LJW) were measured as follows: (1) the medial and lateral edges of the proximal tibia, as well as the midpoint of the intercondylar eminences and the distal shaft of the tibia, were identified and designated. These points were connected, forming the long axis of the tibia. (2) Two separate lines representing each compartment of the knee were drawn. (3) Next, two lines bisecting the midpoints of each compartment of the knee were drawn parallel to the long axis of the tibia. (4) Then, the points at which the midpoint lines met the lowest point of the femoral cortex and the highest point of the tibial cortex were specified by the investigator. (5) Finally, the length of the line connecting these points was defined as the joint space width in each compartment (Fig. 4A) [1]. Knee joint line orientation (KJLO) was defined as the

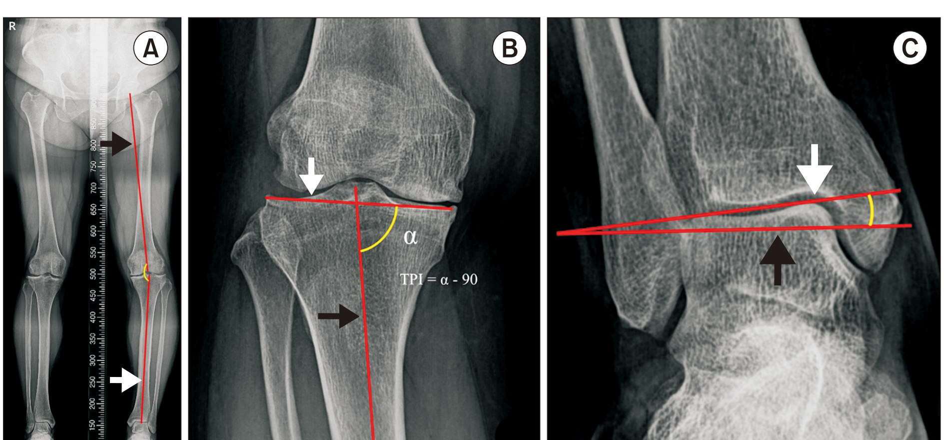

Fig. 3. (A) Hip-knee-ankle angle (HKA): the mechanical axis of the femur (black arrow) and the mechanical axis of the tibia (white arrow). (B) Tibia plateau inclination (TPI): the mechanical axis of the tibia (black arrow), tangent to the subchondral plate of the proximal tibia (white arrow). (C) Ankle joint line orientation (AJLO): tangent to the subchondral plate of the talus (white arrow), horizontal grid line (black arrow).

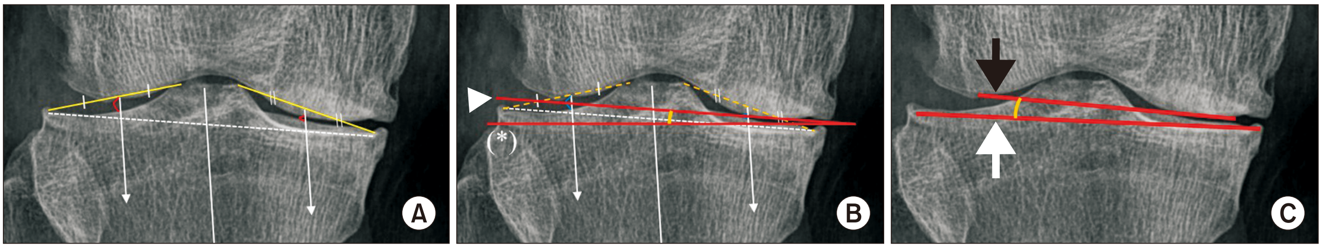

Fig. 4. (A) Medial and lateral joint widths (MJW and LJW): (1) tangent to the subchondral plate of the proximal tibia (white dotted line), (2) the mechanical axis of the tibia (white line), (3) the line between the medial (lateral) end of the tibia plateau and medial (lateral) end point of the intercondylar eminence (yellow line), and (4) the line bisecting the yellow line and parallel to the white line (white line with arrow). The distance between the lowest point of the femoral condyle and the highest point of the tibia plateau is defined as the joint width of each compartment. (B) Knee joint line orientation (KJLO): line connecting the midpoints of the medial and lateral knee joint space (►), horizontal grid line (*). (C) Joint line convergence angle (JLCA): the line tangential to the distal femoral condyle (black arrow) and the tibial plateau (white arrow).

angle between the line connecting the midpoints of the medial and lateral knee joint space and a horizontal grid line on radiographs that was parallel to the floor; a negative value was given when the midjoint space line tilted medially relative to the horizontal grid line (Fig. 4B) [3]. Joint line convergence angle (JLCA) was defined as the angle formed between a line tangential to the distal femoral condyle and the tibial plateau (Fig. 4C) [11].

Correction angle was defined as the angle between the upper and lower borders of the osteotomy site. Correction height was defined as the distance between the upper and lower edges of the opened posteromedial osteotomy site (Fig. 5) [10].

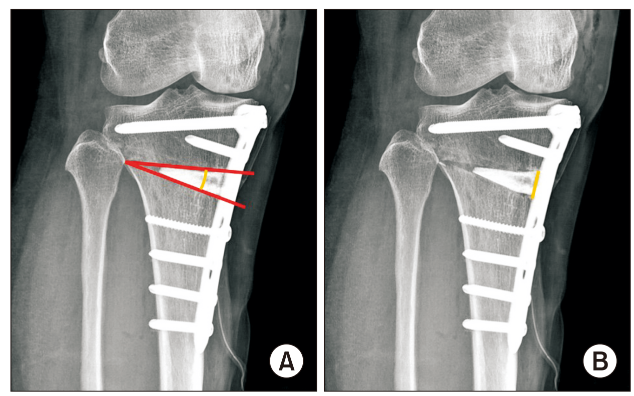

Fig. 5. (A) Correction angle and (B) correction height.

Clinical score

Additionally, the preoperative and last follow-up postoperative clinical scores were reviewed according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [12] and International Knee Documentation Committee (IKDC) scores [13]. The WOMAC score includes three categories, including pain (five questions), stiffness (two questions), and activity of daily life (17 questions). The maximum score is 96. The IKDC score also includes three categories, including symptoms (seven questions), functions (two questions), and activity level (10 questions). The maximum score is 105.

Statistical analysis

Statistical analyses were performed using SPSS software version 26 (IBM Corp., Armonk, NY, USA). A paired t-test was used for the analysis of pre- and postoperative differences in group H. The Wilcoxon rank sum test was used for the analysis of pre- and postoperative difference in group HS. The Mann–Whitney U test was used for the analysis of differences between the two groups. Statistically significant difference was defined as $P < 0.05$.

RESULTS

Demographics

A total of 58 patients were reviewed, and 14 patients were excluded. Ten patients were excluded because they underwent HTO owing to other diseases other than OA. Four patients were excluded because they had a follow-up period of < 12 months. A total of 44 knees (group H: 32, group HS: 12) were enrolled. The demographic data and characteristics of enrolled patients are presented in Table 1.

Preoperative radiologic parameters

No significant difference in all preoperative radiologic parameters was observed between the two groups (all $P > 0.05$) (Table 2).

Comparison of changes between preoperative and last follow-up radiologic parameters

Significant changes were noted between preoperative and

Table 1. Comparison of demographics of group H and group HS

Variable	Group H[a)] (n = 32)	Group HS[b)] (n = 12)	P-value
Age (y)	57.2	55.1	0.153
Sex			0.651
Male	6	3	
Female	26	9	
Height (cm)	157.3	159.4	0.117
Weight (kg)	67.3	65.4	0.084
Mean follow-up period (mo)	19.8	30.4	0.002
BMI (kg/m^2)	27.22	25.67	0.091

Values are presented as mean only or number only.
BMI, body mass index; HTO, high tibial osteotomy; hUCB-MSC, human umbilical cord blood-derived mesenchymal stem cell.
[a)]Patients who underwent HTO only.
[b)]Patients who underwent HTO with cartilage regeneration surgery using hUCB-MSCs.
Statistically significant, P < 0.05.

Table 2. Comparison of preoperative radiologic parameters between both groups

Variable	Group H[a)] (n = 32)	Group HS[b)] (n = 12)	P-value
HKA (°)	–8.28	–7.79	0.536
TPI (°)	–4.94	–5.34	0.527
KJLO (°)	–1.86	–2.76	0.174
AJLO (°)	8.31	6.67	0.421
MJW (mm)	4.17	4.62	0.108
LJW (mm)	6.55	6.11	0.274
JLCA (°)	–3.72	–3.14	0.544

Values are presented as mean only.
HKA, hip-knee-ankle angle; TPI, tibia plateau inclination; KJLO, knee joint line orientation; AJLO, ankle joint line orientation; MJW, medial joint width; LJW, lateral joint width; JLCA, joint line convergence angle; HTO, high tibial osteotomy; hUCB-MSC, human umbilical cord blood-derived mesenchymal stem cell.
[a)]Patients who underwent HTO only.
[b)]Patients who underwent HTO with cartilage regeneration surgery using hUCB-MSCs.
Statistically significant, P < 0.05.

last follow-up radiologic parameters except for the medial joint width in both groups (MJW: group H, P = 0.207; group HS, P = 0.272). However, the differences between the last follow-up postoperative radiologic parameter and preoperative radiologic parameter in the two groups were not statistically significant (all P > 0.05) (Table 3).

Comparison of changes between 6 months postoperative and last follow-up radiologic parameters

No statistically significant difference was noted between the 6-month postoperative radiologic parameter and the last follow-up radiologic parameter except for KJLO in the two groups (P = 0.005) (Table 4). The average KJLO decreased by 0.49° in group H. Conversely, it increased to 1.18° in group HS.

Table 3. Comparison of changes between preoperative and last follow-up radiologic parameters

Variable	Group H[a)] (n = 32)	Group HS[b)] (n = 12)	P-value
HKA (°)	11.49	10.48	0.349
TPI (°)	8.15	8.88	0.518
KJLO (°)	3.64	4.95	0.316
AJLO (°)	–8.28	–7.44	0.598
MJW (mm)	–0.20	–0.30	0.645
LJW (mm)	–1.11	–1.24	0.813
JLCA (°)	2.61	2.06	0.553

Values are presented as mean only.
HKA, hip-knee-ankle angle; TPI, tibia plateau inclination; KJLO, knee joint line orientation; AJLO, ankle joint line orientation; MJW, medial joint width; LJW, lateral joint width; JLCA, joint line convergence angle; HTO, high tibial osteotomy; hUCB-MSC, human umbilical cord blood-derived mesenchymal stem cell.
[a)]Patients who underwent HTO only.
[b)]Patients who underwent HTO with cartilage regeneration surgery using hUCB-MSCs.
Statistically significant, P < 0.05.

Table 4. Comparison of changes between 6 months postoperative and last follow-up radiologic parameters

Variable	Group H[a)] (n = 32)	Group HS[b)] (n = 12)	P-value
HKA (°)	0.14	0.78	0.280
TPI (°)	–0.20	0.40	0.919
KJLO (°)	–0.49	1.18	0.005
AJLO (°)	–0.25	1.61	0.053
MJW (mm)	0.35	0.36	0.843
LJW (mm)	0.25	0.13	0.782
JLCA (°)	0.59	0.02	0.192

Values are presented as mean only.
HKA, hip-knee-ankle angle; TPI, tibia plateau inclination; KJLO, knee joint line orientation; AJLO, ankle joint line orientation; MJW, medial joint width; LJW, lateral joint width; JLCA, joint line convergence angle; HTO, high tibial osteotomy; hUCB-MSC, human umbilical cord blood-derived mesenchymal stem cell.
[a)]Patients who underwent HTO only.
[b)]Patients who underwent HTO with cartilage regeneration surgery using hUCB-MSCs.
Statistically significant, P < 0.05.

Clinical scores

No significant difference in the preoperative WOMAC and

Table 5. Comparison of clinical outcome improvement between both groups

Variable	Group H[a)] (n = 32)	Group HS[b)] (n = 12)	P-value
IKDC			
Preoperative	41.8	46.7	0.059
Last follow-up	76.2	82.8	0.544
WOMAC			
Preoperative	46.6	52.8	0.089
Last follow-up	80.6	84.3	0.916

Values are presented as mean only.
IKDC, International Knee Documentation Committee; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; HTO, high tibial osteotomy; hUCB-MSC, human umbilical cord blood-derived mesenchymal stem cell.
[a)]Patients who underwent HTO only.
[b)]Patients who underwent HTO with cartilage regeneration surgery using hUCB-MSCs.
Statistically significant, $P < 0.05$.

IKDC scores was observed between the two groups ($P > 0.05$).

Significant improvement in the last follow-up postoperative WOMAC score ($P = 0.003$) and IKDC score ($P = 0.002$) was observed compared with the preoperative score in both groups, respectively. However, no significant differences in clinical scores at the last follow-up were observed between the two groups (all $P > 0.05$) (Table 5).

DISCUSSION

This study suggested that there was no difference between the two groups generally. However, a significant difference in changes between 6 months postoperative and the last follow-up KJLO was noted. It decreased in group H and increased in group HS, suggesting that valgus alignment after HTO with cartilage regeneration surgery was well maintained compared with that after HTO only. Although no difference in MJW between the two groups was noted, we believed that the remodeled cartilage can take the role of cushion between the medial femoral condyle and the tibia plateau.

Several surgeons have attempted an additional cartilage remodeling or regeneration procedure after reducing pressure on the medial compartment of the knee by HTO. Various outcomes are derived after cartilage regeneration surgery concomitant with HTO. Kahlenberg et al. [14] reviewed 827 patients who underwent HTO with a cartilage restoration technique, such as micro-fracture, PRP, osteochondral autograft transfer, and autologous chondrocyte implantation, and concluded that HTO with cartilage restoration procedures provides reliable improvement in functional status in the medium- to long-term period. Wong et al. [15] suggested that HTO with bone marrow-derived MSC injection is effective for improving clinical outcomes. In this study, the HTO with MSC injection group showed significantly better Tegner, Lysholm, and IKDC scores than the HTO only group [15]. One meta-analysis analyzed 15 studies about MSC implantation with HTO, suggesting that MSC implantation may improve arthroscopic and histologic outcomes although no beneficial effect on clinical outcomes was noted on radiograph [16]. Another meta-analysis that analyzed four studies and included 224 patients (111 and 113 patients in the MSC and control groups, respectively) reported that MSC augmentation produced similar radiological outcomes and small but significant improvement in functional outcomes [17].

In our study, the HTO with cartilage regeneration surgery group showed better clinical scores than the HTO only group. However, no statistical significance was noted. The different mean follow-up periods between the two groups can be one of the causes. Furthermore, a study with long-term follow-up is needed.

Additionally, several researchers have reported magnetic resonance imaging (MRI) outcome and second-look arthroscopy after cartilage regeneration surgery. Moreover, several studies have reported satisfactory MRI outcomes based on modified magnetic resonance observation of cartilage repair tissue (M-MOCART) after cartilage regeneration surgery [7,15,18–20]. Although MRI outcomes showed good results, some studies have mentioned that MRI cannot accurately determine the status of cartilage regeneration [21]. In this study, it was determined that second-look arthroscopy should be performed to verify the condition of the repaired cartilage. Ryu et al. [7] reported significant improvement in the ICRS repair score in patients who underwent HTO with cartilage regeneration surgery using hUCB-MSC or BMAC. In addition, Song et al. [8] reported that the cartilage was regenerated to ICRS grade 3 or better in all patients who underwent HTO with hUCB-MSC implantation. MRI was not performed on all patients; therefore, we did not analyze MRI outcomes in our study. Some patients underwent MRI follow-up after removal of internal fixation device and showed improvement in cartilage status; therefore, we are planning to conduct an additional study about MRI outcomes after HTO with cartilage regeneration surgery.

However, some studies claimed that although cartilage regeneration improved the ICRS repair score, the repaired cartilage was composed of mixed repair (hyaline cartilage and fibrocartilage) [22]. Others reported that the repaired cartilage was composed of hyaline-like cartilage [23,24]. Despite controversy in the cartilage status, it is certain that HTO with cartilage regeneration surgery showed significant improvement in clinical outcomes and M-MOCART. Song et al. [18] followed up 128 patients at least 2 years after HTO with cartilage regeneration surgery and claimed that clinical scores (visual analog scale [VAS], WOMAC, and IKDC scores) and M-MOCART were significantly improved after HTO with cartilage regeneration surgery.

This study had several limitations. First, this study had a retrospective study design, relatively short-term follow-up results, and small sample size. Particularly, group HS included a small number of patients. In addition, a significant difference in the follow-up period between group H and group HS was noted. The difference can cause bias in terms of radiologic parameters. Second, we did not distinguish candidates of additional hUCB-MSCs implantation concomitant with HTO based on cartilage status or size of cartilage defect. Grossly, no difference in the cartilage status between group H and group HS was noted. However, because there was lack of exact records about classified cartilage status in group H, we could not compare group H with group HS. Third, second-look arthroscopy and postoperative MRI study were not performed owing to the short-term follow-up period. We are performing postoperative MRI in patients who underwent removal of an internal fixation device. Nevertheless, the strength of our study lies in the comparison of comprehensive simple radiologic parameters between the HTO only group and the HTO with cartilage regeneration surgery group.

Both groups showed satisfactory clinical and radiological outcomes in short-term follow-up. However, no difference was observed between the two groups. In the future, a study with medium- to long-term follow-up is needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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