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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells* (*WJSC*, *World J Stem Cells*) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

 WJSC publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryoid bodies, embryonal carcinoma stem cells, hemangioblasts, hematopoietic stem cells, lymphoid progenitor cells, myeloid progenitor cells, *etc*.

INDEXING/ABSTRACTING

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RESPONSIBLE EDITORS FOR THIS ISSUE

Retrospective Study

High tibial osteotomy with human umbilical cord blood-derived mesenchymal stem cells implantation for knee cartilage regeneration

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Abstract

BACKGROUND
High tibial osteotomy (HTO) is a well-established method for the treatment of medial compartment osteoarthritis of the knee with varus deformity. However, HTO alone cannot adequately repair the arthritic joint, necessitating cartilage regeneration therapy. Cartilage regeneration procedures with concomitant HTO are used to improve the clinical outcome in patients with varus deformity.

AIM
To evaluate cartilage regeneration after implantation of allogenic human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) with concomitant HTO.

METHODS
Data for patients who underwent implantation of hUCB-MSCs with concomitant HTO were evaluated. The patients included in this study were over 40 years old, had a varus deformity of more than 5°, and a full-thickness International Cartilage Repair Society (ICRS) grade IV articular cartilage lesion of more than 4 cm^2 in the medial compartment of the knee. All patients underwent second-look arthroscopy during hardware removal. Cartilage regeneration was evaluated macroscopically using the ICRS grading system in second-look arthroscopy. We also assessed the effects of patient characteristics, such as trochlear lesions, age, and lesion size, using patient medical records.

RESULTS

A total of 125 patients were included in the study, with an average age of 58.3 ± 6.8 years (range: 43-74 years old); 95 (76%) were female and 30 (24%) were male. The average hip-knee-ankle (HKA) angle for measuring varus deformity was 7.6° ± 2.4° (range: 5.0-14.2°). In second-look arthroscopy, the status of medial femoral condyle (MFC) cartilage was as follows: 73 (58.4%) patients with ICRS grade I, 37 (29.6%) with ICRS grade II, and 15 (12%) with ICRS grade III. No patients were staged with ICRS grade IV. Additionally, the scores [except International Knee Documentation Committee (IKDC) at 1 year] of the ICRS grade I group improved more significantly than those of the ICRS grade II and III groups.

CONCLUSION

Implantation of hUCB-MSCs with concomitant HTO is an effective treatment for patients with medial compartment osteoarthritis and varus deformity. Regeneration of cartilage improves the clinical outcomes for the patients.

Key words: Allogeneic; Human umbilical cord blood-derived mesenchymal stem cells; Cartilage regeneration; High tibial osteotomy; Osteoarthritic knees; Arthroscopy

Core tip: This is the first study to evaluate clinical outcomes and cartilage regeneration *via* second-look arthroscopy after implantation of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) with concomitant high tibial osteotomy (HTO) for treatment of osteoarthritic knee with varus deformity. HTO treatment of medial compartment osteoarthritis of the knee with varus deformity alone does not sufficiently repair arthritic joints. However, HTO decreases pressure in the medial compartment, providing an environment in which damaged cartilage can be regenerated *via* implantation of allogenic hUCB-MSCs. hUCB-MSC implantation with HTO is an effective treatment for patients with osteoarthritis of the knee with varus deformity, leading to improved clinical outcomes.

INTRODUCTION

Increased load bearing on the medial compartment of the knee joint in varus deformity, abnormally activates chondrocytes, osteoblasts, and synoviocytes. These cells, then, aberrantly secrete several inflammatory-response proteins and matrix-degrading enzymes, thereby contributing to the gradual progression of medial compartment osteoarthritis (MCOA)[1-4]. High tibial osteotomy (HTO), a well-established method for treating MCOA, provides an environment in which damaged cartilage can be regenerated *via* decreased medial compartment pressure[5-7]. HTO alone offers excellent short- and mid-term outcomes, however, these outcomes tend to deteriorate over time[6-10]. Cartilage regeneration procedures, such as microfracture (MFx) and autologous chondrocyte implantation (ACI) with concomitant HTO, may improve long-term outcomes in this patient population[11-17]. Although MFx and ACI are widely used for cartilage regeneration, they are not suitable for osteoarthritis (OA) therapy[18-20].

Injection or implantation of mesenchymal stem cells (MSCs) with concomitant HTO has been reported to regenerate cartilage in MCOA[21-24]. MSCs can be obtained from the bone marrow (BM), synovium, adipose tissue, and umbilical cord. These cells possess anti-inflammatory, anti-apoptotic, and anti-fibrotic properties. Moreover, MSCs facilitate chondrogenesis, demonstrate a remarkable safety profile without tumorigenecity, and have been shown to improve clinical outcomes in patients with OA[25-31]. Among the variously sourced MSCs, human umbilical cord blood-derived MSCs (hUCB-MSCs) have shown superior cartilage repair without bone formation or

degeneration of the repaired cartilage[32-34]. hUCB-MSCs are additionally advantageous because of their high expansion capacity, non-invasive harvesting, and hypo-immunogenicity. Moreover, as hUCB-MSCs are an allogeneic cell source, they are produced as an off-the-shelf product, and can supply sufficiently high numbers of pure stem cells with respect to the cartilage defect area being treated[35-37]. However, reports on the clinical application of hUCB-MSCs are scarce, and no studies have examined the use of hUCB-MSCs with concomitant HTO[38,39].

To demonstrate whether regenerated cartilage affects clinical outcomes, herein we retrospectively evaluated clinical outcomes and cartilage regeneration *via* second-look arthroscopy following implantation of hUCB-MSCs with concomitant HTO. In addition, we investigated whether patient characteristics, such as articular cartilage lesions on the patellofemoral joint, age, and cartilage defect size, influence clinical outcomes.

MATERIALS AND METHODS

Participants and study design
We retrospectively reviewed the medical records of patients who underwent second-look arthroscopy during hardware removal after receiving implantation of hUCB-MSCs with concomitant HTO for the treatment of MCOA between January 2014 and November 2016. The study protocol was approved by the institutional review board of Korea Ministry of Health and Welfare (2019-3100-003). The patients included in this study were over 40 years old, and had a varus deformity of more than 5° and a full-thickness International Cartilage Repair Society (ICRS) grade IV articular cartilage lesion of more than 4 cm^2 in the medial compartment of the knee[40] (Figures 1 and 2A). Patients with grade IV OA of the medial compartment (identified by radiological assessment according to Kellgren and Lawrence system[41]), knee ligament injuries, metabolic arthritis, joint infections, and articular cartilage lesions at the lateral compartment were excluded. Herein, we evaluated clinical outcomes 3 years post-surgery and assessed cartilage regeneration *via* second-look arthroscopy. Effects of regenerated cartilage on clinical outcomes were evaluated after classification according to the ICRS grading system. We also assessed the effects of patient characteristics such as patient age, presence of a trochlear lesion, and lesion size of medial femoral condyle (MFC) from the patient's medical records.

Preparation of hUCB-MSCs
CARTISTEM® (Medipost, Seongnam-si, Gyeonggi-do, South Korea), an off-the-shelf medicinal product for cartilage regeneration, was used in the study. This product, which consists of 1.5 mL hUCB-MSCs (7.5×10^6 cells/vial) and 4% hyaluronic acid (HA) hydrogel, was approved for cartilage regeneration by the Korea Food and Drug Administration in January 2012. The therapeutic dose is 500 µL/cm^2 as specified in the manufacturer's instructions. Preoperatively, the cartilage defect size was measured by magnetic resonance imaging (MRI), and the therapeutic dose was determined. After combining hUCB-MSCs with 4% HA hydrogel using a spatula, the mixture was transferred into a 5-mL syringe for implantation into the defect.

Surgical procedure and postoperative management
All surgical procedures, including diagnostic arthroscopy, synovectomy, excision of degenerative menisci tears, microfracture, and HTO, were performed by a single surgeon. After completion of the arthroscopic procedure, the fluid was washed out, and arthroscopic instruments were removed from the joint. A 5-7 cm longitudinal incision was made on the medial parapatellar area, and the medial femoral condyle (MFC) was exposed by dissecting the medial patellofemoral ligament and joint capsule. The damaged cartilage was removed using a curette, and sclerotic bone on the surface of the femoral condyle was removed using a burr. For implantation of hUCB-MSCs, multiple holes (4 mm in diameter and 4 mm in depth) were made in cartilage defects, and the space between the holes was drilled using a 2-mm-thick Kirschner wire. Irrigation was used to remove intra-articular debris. The hUCB-MSC and HA hydrogel mixture was then implanted into the holes and articular surface (Figure 3A-C). After implantation of hUCB-MSC, open-wedge HTO was performed using an anatomical locking metal-block plate (Ohtofix; Ohtomedial CO. Ltd., Goyang-si, South Korea)[42]. All knees underwent uniplanar osteotomy aiming to correct the mechanical axis to approximately 62% lateral to the tibial plateau[43] (Figure 2B). After surgery, patients were encouraged to perform isometric quadricep/hamstring exercise and straight leg-raises, however, knee flexion was limited to 90° for 4 wk. Partial weight-bearing began after 4 wk, and full weight-
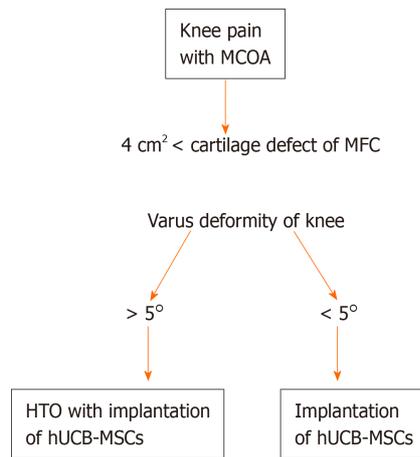
Figure 1 Flow chart of selection criteria. MCOA: Medial compartment osteoarthritis; MFC: Medial femoral condyle; HTO: High tibial osteotomy; hUCB-MSCs: Human umbilical cord blood-derived mesenchymal stem cells.

bearing was permitted at week 6.

Clinical outcome assessment

The clinical outcomes of all patients were evaluated preoperatively, as well as at 1 year, 2 years, and 3 years postoperatively. The guidelines of the International Knee Documentation Committee (IKDC) were used to evaluate knee function and sport activity[44], while the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was used to evaluate OA[45]. Scores obtained using visual analog scales (VAS) were also used to assess pain.

Cartilage regeneration evaluation using second-look arthroscopy

All patients underwent second-look arthroscopy during hardware removal. Cartilage regeneration was evaluated macroscopically using the ICRS grading system in second-look arthroscopy[40]. According to the ICRS grading system, grade I is considered normal, grade II considered nearly normal, grade III abnormal, and grade 4 severely abnormal.

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, United States) with significance defined as $P < 0.05$. All data are presented as the mean ± standard deviation. IKDC, WOMAC, and VAS scores were applied as the primary dependent variables in clinical outcomes. Wilcoxon signed-rank test was performed to compare the preoperative and postoperative state of articular cartilage in the patient cohort. Kruskal-Wallis test was performed to compare three or more variables. Mann-Whitney U test with Bonferroni adjustment was used for post-hoc comparison. Mann-Whitney U test was used to compare cartilage regeneration in patients with trochlear lesions *vs* patients without trochlear lesions. Simple regression analysis was performed to identify the effects of age and lesion size on clinical outcomes. The statistical methods used in this study were reviewed by Dr. Young Ju Kim from the Department of Statistics at the Catholic University of Korea.

RESULTS

In this study, 125 patients with an average age of 58.3 ± 6.8 years (range: 43-74 years old) were included, of whom 95 (76%) were female and 30 (24%) were male. The average body mass index (BMI) was 25.6 ± 2.7 kg/m² (range: 19.2-35.5 kg/m²) and average hip-knee-ankle (HKA) angle for measuring varus deformity was 7.6° ± 2.4° (range: 5.0°-14.2°). Seventy-three (58.4%) patients had trochlear lesions, while the remaining 52 (41.6%) did not (Table 1).

Second-look arthroscopic findings

Postoperative second-look arthroscopy with hardware removal was performed at 20.2 ± 6.5 mo (range: 8-38 mo) post-surgery. In second-look arthroscopy, the MFC cartilage status was as follows: 73 (58.4%) patients with ICRS grade I, 37 (29.6%) with ICRS grade II, and 15 (12%) with ICRS grade III. No patients had ICRS grade IV (Figure 4A-F) (Table 1).

Figure 2 High tibial osteotomy. A: High tibial osteotomy was performed at a hip-knee-ankle angle of 5° or more; B: The mechanical axis was corrected to approximately 62% lateral to the tibial plateau.

Clinical outcome according to the ICRS grading system

Clinical results were analyzed by classifying patient groups according to the ICRS grading system. In the ICRS grade I group, the preoperative IKDC score was 28.4 ± 7.4 (rang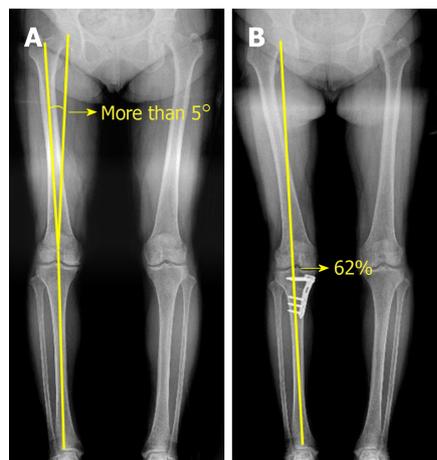e: 10.3–43.7) and increased to 59.3 ± 8.7 (range: 40.8–82.8), 64.3 ± 9.2 (range: 44.8-90.8), and 68.1 ± 10.8 (range: 40.2–90.8) at 1-, 2-, and 3-year follow-up, respectively (P < 0.001 for both 1- and 2-year follow-up; P = 0.001 for the final follow-up). The WOMAC score decreased from 45.1 ± 11 (range: 22-79) preoperatively to 11.0 ± 6.9 (range: 2–39), 8.4 ± 6.0 (range: 0-28), and 6.5 ± 6.0 (range: 0-33) at 1-, 2-, and 3-year follow-up, respectively (P < 0.001 for both 1- and 2-year follow-up; P = 0.003 at 3-year follow-up). The VAS score also decreased from 7.6 ± 1.4 (range: 4–10) preoperatively to 2.1 ± 1.7 (range: 0–7), 1.5 ± 1.4 (range: 0-6), and 1.1 ± 1.5 (range: 0-33) at 1-, 2-, and 3-year follow-up, respectively (P < 0.001 at both 1- and 2-year follow-up; P = 0.004 at 3-year follow-up).

All clinical outcomes in the ICRS grade I group improved significantly over time. In the ICRS grade II group, the IKDC score increased from 30.1 ± 7.2 (range: 16.1-54.0) preoperatively to 52.4 ± 10.7 (range: 29.9-70.1), 58.6 ± 11.1 (range: 40.5-82.8), and 61.0 ± 11.3 (range: 43-90.8) at 1-, 2-, and 3-year follow-up, respectively (P < 0.001 for both 1- and 2-year follow-up; P = 0.063 for 3-year follow-up). The WOMAC score decreased from 41.9 ± 9.2 (range: 30-64) preoperatively to 16.8 ± 8.5 (range: 5-40), 13.4 ± 8.2 (range: 1–39), and 10.5 ± 5.6 (range: 0-22) at 1-, 2-, and 3-year follow-up, respectively (P < 0.001 for 1-year follow-up; P = 0.001 for 2-year follow-up; P = 0.002 for 3-year follow-up). The VAS score decreased from 7.5 ± 1.1 (range: 6-10) preoperatively to 3.0 ± 1.6 (range: 0–7), 2.7 ± 1.8 (range: 0–8), and 2.0 ± 1.4 (range: 0-4) at 1- (P < 0.001), 2- (P= 0.229), and 3-year (P = 0.019) follow-up, respectively. In the ICRS grade III group, the IKDC score increased from 29.2 ± 8.1 (range: 11.4-43.6) preoperatively to 54.8 ± 7.1 (range: 45.2–70.1), 55.0 ± 8.0 (range: 40.4-75.9), and 59.3 ± 5.8 (range: 45.8–72.4) at 1-, 2-, and 3-year follow-up, respectively (P = 0.001, P = 0.842, and P = 0.047, respectively). The WOMAC score decreased from 44.3 ± 12.2 (range: 29–76) preoperatively to 17.6 ± 5.1 (range: 10–26), 17.3 ± 7.4 (range: 4–30), and 12.6 ± 8.3 (range: 1–28) at 1-, 2-, and 3-year follow-up, respectively (P = 0.001, P = 0.607, and P = 0.018, respectively). The VAS score decreased from 7.7 ± 0.8 (range: 6–9) preoperatively to 3.3 ± 1.2 (range: 1–6), 3.1 ± 1.2 (range: 1–5), and 2.6 ± 0.9 (range: 1–4) at 1-, 2-, and 3-year follow-up, respectively (P = 0.001, P = 0.658, and P = 0.103, respectively).

Preoperative scores showed no significant differences among the groups of patients (IKDC, WOMAC, and VAS; P = 0.610, P = 0.275, and P = 0.817, respectively). However, postoperative scores showed significant differences among patient groups at all the time points of follow-up (IKDC score: P = 0.005 at 1 year, and P < 0.001 at 2 and 3 years; WOMAC score: P < 0.001 at all follow-up time points; VAS score: P = 0.002 at 1 year, P < 0.001 at 2 and 3 years). Post hoc analysis revealed that except for IKDC at 1 year, all scores in the ICRS grade I group improved more than those of the ICRS grade II and III groups; IKDC scores of the ICRS grade II group did not differ significantly from those of the ICRS grade III group. The IKDC score of the ICRS grade I group differed significantly from that of the ICRS grade II group at 1-year follow-up; however, IKDC scores of other groups did not differ significantly at 1-year follow-up (Table 2).
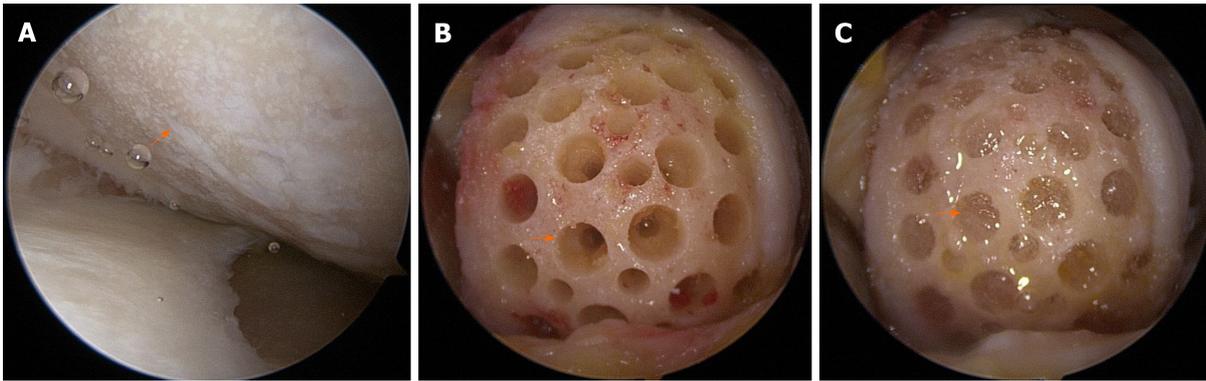
Figure 3 Arthroscopic findings of stem cell implantation procedures. A: Medial compartment osteoarthritis (arrow) in a 61-year-old woman; B: Multiple holes, 4 mm in diameter and 4 mm in depth (arrow), were drilled using a drill bit; C: Human umbilical cord blood-derived mesenchymal stem cells were mixed with hyaluronic acid hydrogel and implanted in the holes (arrow).

Clinical outcomes according to patient characteristics
Preoperative VAS scores differed significantly between the trochlear lesion group and the non-lesion group (P = 0.046); however, no significant differences in outcomes observed between these two groups at 1, 2, and 3 years postoperatively (P > 0.05 for all time points) (Table 3). Similarly, the WOMAC and IKDC scores did not differ significantly between the trochlear lesion group and the non-lesion group (P > 0.05 for all time points). The preoperative WOMAC score increased with increasing age (P < 0.001) but did not affect other outcomes (P > 0.05 for all). The lesion size of the MFC did not affect the IKDC score (P > 0.05 for all follow-up time points). The preoperative WOMAC score increased significantly with increased lesion size but did not affect the postoperative WOMAC score (P < 0.001 for preoperative WOMAC, and P > 0.05 for postoperative WOMAC). The VAS score increased significantly with increased lesion size at the preoperative stage (P < 0.001). However, there was no significant difference in postoperative outcomes (P > 0.05) (Table 4).

DISCUSSION

The results obtained in this study show that cartilage was regenerated to ICRS grade III or better in all cases after implantation of hUCB-MSCs with concomitant HTO. Jung *et al*[7] showed that cartilage was regenerated in MFC and MTP in second-look arthroscopy after medial opening-wedge HTO without any cartilage regeneration surgery. Although regenerated cartilage is mostly immature, we believe that reduced joint loading of the medial compartment after HTO provides an environment in which cartilage is regenerated. Accordingly, implantation or injection of MSCs with concomitant HTO has been used to enhance insufficient cartilage regeneration. Wong *et al*[23] investigated the injection of BM-derived MSCs with HA 3 weeks after MFx with HTO. They reported improved short-term outcomes, as well as magnetic resonance observation of cartilage repair tissue (MOCART) scores compared with those of the control group. Koh *et al*[24] compared a group treated with an injection of platelet-rich plasma (PRP) and concomitant HTO to a group treated with a dose of platelet-rich plasma (PRP), HTO, and an additional infusion of adipose-tissue-derived MSCs. Their results demonstrated that the group receiving MSC injection showed improved cartilage recovery and clinical outcomes compared with the group receiving a PRP injection only[24]. Kim *et al*[22] confirmed that injection of adipose tissue-derived MSCs in 50 patients of MCOA improved clinical outcomes more than did HTO alone. Although we have not included a control group, we show that regenerated cartilage affected clinical outcomes in patients with varus deformity of more than 5° and full-thickness articular cartilage lesion of ICRS grade IV with more than 4 cm^2 in the medial compartment of the knee.

Regenerated cartilage in the ICRS grades I, II, and III groups improved the clinical outcomes of these patients, with the ICRS grade I group showing the best clinical outcomes among the three groups. Indeed, all scores in the ICRS grade I group improved over time compared with those of the ICRS grade II and III groups. These results indicate that cartilage regeneration *via* hUCB-MSCs implantation with concomitant HTO, is an effective approach to cartilage regeneration. In our present study, the regeneration status of articular cartilage in 73 (58.4%) patients, assessed *via* second-look arthroscopy, was judged to be ICRS grade I and accounted for the largest

Table 1 Patient demographic data	
Patients	*n* = 125
Age, yr	58.3 ± 6.8
Sex, female/male	95 (76%)/30 (24%)
Lesion size, cm^2	6.9 ± 2
HKA angle, degree	7.6 ± 2.4
Trochlear lesion	
With lesion	73
Without lesion	52
Second look arthroscopic findings	
ICRS grade I	73
ICRS grade II	37
ICRS grade III	15

HKA: Hip-knee-ankle; ICRS: International Cartilage Repair Society.

proportion of the patients. Although some patients presented with partially regenerated cartilage, none showed a lack of cartilage regeneration (ICRS grade IV). We did not perform a histological examination to avoid damaging the regenerated cartilage in these patients. However, in patients with large chondral lesions, the regenerated cartilage fully covered the lesions, and showed adequate thickness and elasticity as assessed *via* palpation with a probe during second-look arthroscopy. Similarly, Park *et al*[38] reported that hyaline-like cartilage was regenerated after hUCB-MSCs implantation in patients with OA, resulting in improved clinical outcomes in these patients.

Although the mechanisms involved in hUCB-MSC-mediated cartilage regeneration are only partially characterized[46-48], it is clear that hUCB-MSC-based strategies are effective in treating patients with OA. Allogeneic hUCB-MSCs are not only standardized as off-the-shelf medicinal products, but also non-invasively yield a sufficient number of stem cells that can be applied according to the size of the cartilage lesion. Jo *et al*[49] reported that patients with OA showed reduced pain levels and improved function after being treated with a high dose of adipose tissue-derived MSCs (1.0×10^8 cells) compared with a low (1.0×10^7 cells) or moderate dose (5.0×10^7 cells) administered intra-articularly. In addition, the cartilage defect area was regenerated into hyaline-like cartilage in the high dose group. However, the number of stem cells with respect to defect sizes has not been standardized and requires further investigation.

We also investigated whether patient age, presence of trochlear lesion, and size of lesion of MFC influenced clinical outcomes in patients with varus deformity. Several studies have shown that although OA is exacerbated by increased pressure in the patellofemoral (PF) joint after HTO, this process does not deteriorate clinical results or affect anterior knee pain[50,51]. In our present study, patients with trochlear lesions showed significantly increased preoperative VAS scores compared to those without trochlear lesions; however, there were no differences in other scores between these two patient groups. The results of our present study show that implantation of hUCB-MSCs into the trochlea exerted a positive effect on cartilage regeneration. However, further studies are required to evaluate cartilage regeneration in the trochlea after hUCB-MSCs implantation with concomitant HTO. Furthermore, the preoperative WOMAC scores were the only variable affected by advanced patient age. Autologous sources of MSCs such as adipose tissue and BM are age-dependent[52-54]; however, hUCB-MSCs maintain cell quality regardless as it is a cell therapy product. Finally, increased lesion size caused a subsequent increase in the preoperative VAS and WOMAC scores, but it did not affect other postoperative scores. These results indicate that implantation of hUCB-MSCs with concomitant HTO was applicable in patients with trochlear lesions and may even be a viable treatment option in patients with older or more extensive lesions.

Certain limitations were noted in this study. First, it was retrospective and did not include a control group. However, the presence of regenerated cartilage was confirmed *via* second-look arthroscopy in all the 125 patients. We also evaluated how the status of regenerated cartilage affected clinical outcomes. Thus, we can suggest the necessity of cartilage repair procedure during HTO. Second, although the presence of regenerated cartilage was confirmed visually and palpated using a probe, it was not
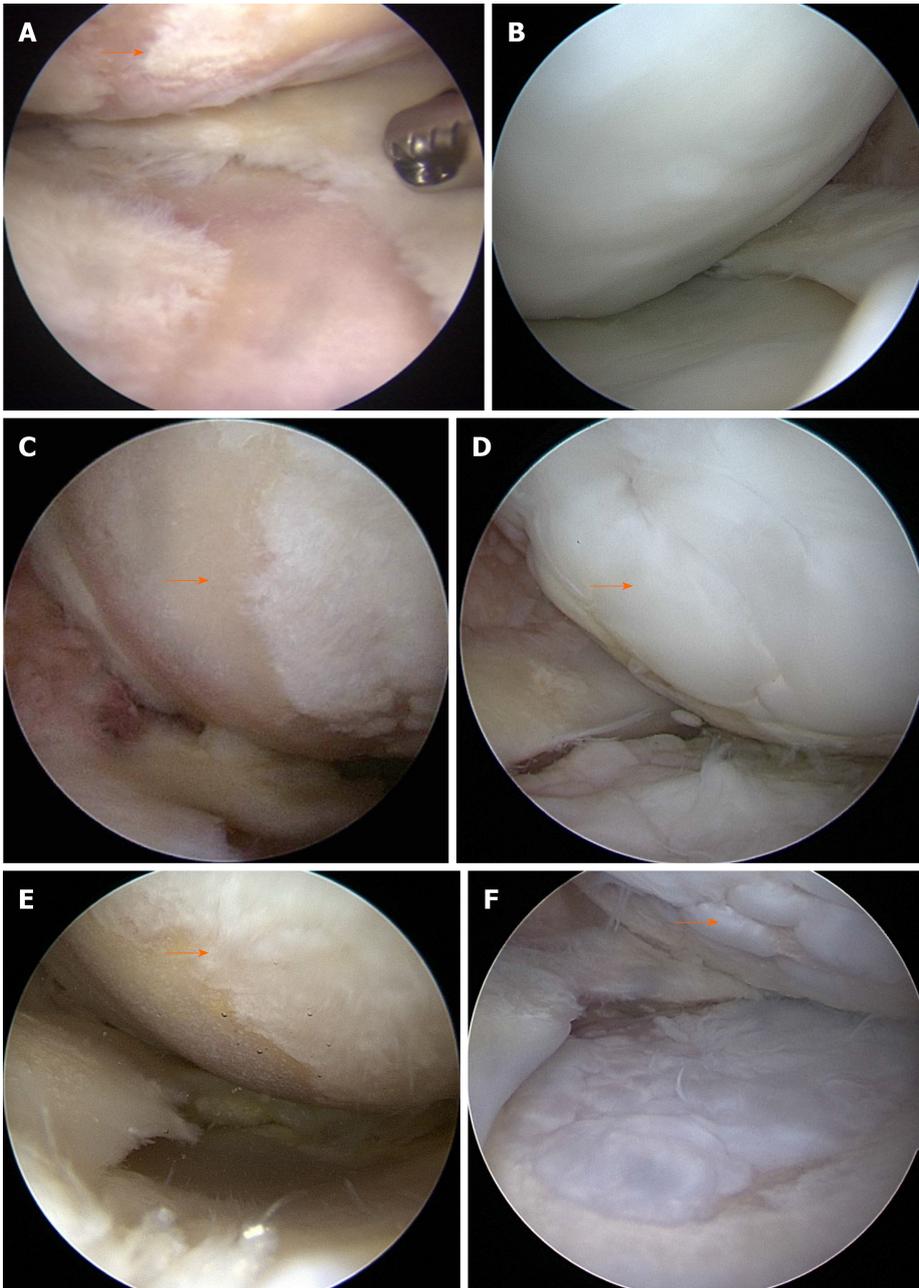
Figure 4 Second-look arthroscopic findings. A: Cartilage lesions classified as International Cartilage Repair Society (ICRS) grade IV in the medial femoral condyle (MFC) (arrow) and tibial plateau in a 61-year-old female patient; B: Cartilage was regenerated to ICRS grade I (arrow) via second-look arthroscopy, performed 13 mo after the initial operation; C: A cartilage lesion classified as ICRS grade IV in the MFC (arrow) of a 52-year-old male patient; D: Cartilage was regenerated to ICRS grade II (arrow) via second-look arthroscopy, performed 22 mo after the initial operation; E: A cartilage lesion of ICRS grade IV in the MFC (arrow) of a 68-year-old female patient; F: Cartilage was regenerated to ICRS grade III (arrow) via second-look arthroscopy, performed 16 mo after the initial operation.

evaluated histologically as that would have required a biopsy, which could damage the regenerated cartilage. Finally, a second-look arthroscopy was performed during hardware removal at an average time of 20.2 ± 6.5 mo post-surgery. This was a relatively short-term evaluation considering that cartilage remodeling requires an extended period of time. However, reducing the pressure in the medial compartment *via* HTO would preserve the regenerated cartilage and allow it to remain intact over time.

In conclusion, our results show that the implantation of hUCB-MSCs with concomitant HTO was an effective treatment option for patients with MCOA. We confirmed that regenerated cartilage improved clinical outcomes in this patient population. In addition, our results suggest that the presence of the trochlear lesions, the advanced age of the patient, or large cartilage lesions did not significantly affect clinical outcomes in patients with MCOA undergoing HTO with hUCB-MSCs implantation.

Table 2 Clinical outcomes according to the International Cartilage Repair Society grading system

	ICRS grade I (*n* = 73)	ICRS grade II (*n* = 37)	ICRS grade III (*n* = 15)	*P* value[1]	Post hoc[5]
IKDC					
Preoperative	28.4 ± 7.4	30.1 ± 7.2	29.2 ± 8.1	0.610	
1 yr	59.3 ± 8.7	52.4 ± 10.7	54.8 ± 7.1	**0.005**	I > II = III,I = III
2 yr	64.3 ± 9.2	58.6 ± 11.1	55.0 ± 8.0	**< 0.001**	I > II = III
3 yr	68.1 ± 10.8	61.0 ± 11.3	59.3 ± 5.8	**< 0.001**	I > II = III
P value[2]	**< 0.001**	**< 0.001**	**0.001**		
P value[3]	**< 0.001**	**< 0.001**	0.842		
P value[4]	**0.001**	0.063	**0.047**		
WOMAC					
Preoperative	45.1 ± 11	41.9 ± 9.2	44.3 ± 12.2	0.275	
1 yr	11.0 ± 6.9	16.8 ± 8.5	17.6 ± 5.1	**< 0.001**	I > II = III
2 yr	8.4 ± 6.0	13.4 ± 8.2	17.3 ± 7.4	**< 0.001**	I > II = III
3 yr	6.5 ± 6.0	10.5 ± 5.6	12.6 ± 8.3	**< 0.001**	I > II = III
P value[2]	**< 0.001**	**< 0.001**	**0.001**		
P value[3]	**< 0.001**	**0.001**	0.607		
P value[4]	**0.003**	**0.002**	**0.018**		
VAS					
Preoperative	7.6 ± 1.4	7.5 ± 1.1	7.7 ± 0.8	0.817	
1 yr	2.1 ± 1.7	3.0 ± 1.6	3.3 ± 1.2	**0.002**	I > II = III
2 yr	1.5 ± 1.4	2.7 ± 1.8	3.1 ± 1.2	**< 0.001**	I > II = III
3 yr	1.1 ± 1.5	2.0 ± 1.4	2.6 ± 0.9	**< 0.001**	I > II = III
P value[2]	**< 0.001**	**< 0.001**	**0.001**		
P value[3]	**< 0.001**	0.229	0.658		
P value[4]	**0.004**	**0.019**	0.103		

Boldface indicates statistical significance (*P* < 0.05).
[1]Kruskal-Wallis test.
[2]Wilcoxon signed-rank test: Preoperative *vs* 1 year postoperatively.
[3]Wilcoxon signed-rank test: 1 year postoperatively *vs* 2 years postoperatively.
[4]Wilcoxon signed-rank test: 2 years postoperatively *vs* 3 years postoperatively.
[5]Bonferroni adjustment using the Mann-Whitney U test. ICRS: International Cartilage Repair Society; IKDC: International Knee Documentation Committee; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; VAS: Visual analog scales.

Table 3 Clinical outcomes according to trochlear lesion

	Trochlear lesion (*n* = 73)	No trochlear lesion (*n* = 52)	*P* value[1]
IKDC			
Preoperative	29.3 ± 7.3	28.5 ± 7.6	0.794
1 yr	56.7 ± 9.7	56.7 ± 9.7	0.960
2 yr	61.6 ± 10.7	61.4 ± 9.5	0.916
3 yr	64.7 ± 11	65.3 ± 11.4	0.493
WOMAC			
Preoperative	44.8 ± 10.3	43.1 ± 11.1	0.288
1 yr	13.8 ± 7.5	13.2 ± 8.2	0.471
2 yr	10.7 ± 6.9	11.3 ± 8.5	0.958
3 yr	8.4 ± 6.4	8.4 ± 6.8	0.755
VAS			
Preoperative	7.8 ± 1.2	7.3 ± 1.3	0.046
1 yr	2.6 ± 1.7	2.3 ± 1.6	0.331
2 yr	2.1 ± 1.5	2.0 ± 1.7	0.555
3 yr	1.6 ± 1.4	1.4 ± 1.6	0.203

Boldface indicates statistical significance (*P* < 0.05).
[1]Mann-Whitney *U* test. IKDC: International Knee Documentation Committee; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index;

VAS: Visual analog scales.

Table 4 Effect of age and lesion size on clinical outcomes

	Age (*n* = 125)				Lesion size (*n* = 125)			
	β	t	R^2	*P* value[1]	β	t	R^2	*P* value[1]
IKDC								
Pre-op	-0.128	-1.429	0.016	0.156	-0.148	-1.661	0.022	0.099
1 yr	-0.095	-1.053	0.009	0.294	-0.025	-0.282	0.001	0.779
2 yr	-0.053	-0.593	0.003	0.554	-0.120	-1.339	0.014	0.183
3 yr	0.049	0.549	0.002	0.584	0.024	0.266	0.001	0.791
WOMAC								
Pre-op	0.327	3.831	0.107	**< 0.001**	0.305	3.550	0.093	**0.001**
1 yr	0.173	1.945	0.030	0.054	0.040	0.440	0.002	0.661
2 yr	-0.005	-0.055	< 0.001	0.956	0.052	0.575	0.003	0.566
3 yr	-0.048	-0.532	0.002	0.595	-0.064	-0.716	0.004	0.475
VAS								
Pre-op	0.115	1.286	0.013	0.201	0.335	3.943	0.112	**< 0.001**
1 yr	0.114	1.278	0.013	0.204	0.113	1.266	0.013	0.208
2 yr	0.001	0.013	<0.001	0.989	0.112	1.249	0.013	0.214
3 yr	-0.047	-0.519	0.002	0.605	0.164	1.842	0.027	0.068

Boldface indicates statistical significance (*P* < 0.05).
[1]Simple regression analysis. Pre-op: Preoperative; IKDC: International Knee Documentation Committee; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; VAS: Visual analog scales.

ARTICLE HIGHLIGHTS

Research background

High tibial osteotomy (HTO) is widely used to treat medial compartment osteoarthritis (MCOA) of the knee with varus deformity. HTO reduces knee pain and improves knee function by decreasing the pressure in the medial compartment of the knee.

Research motivation

HTO alone offers excellent short- and mid-term outcomes; however, these outcomes tend to deteriorate over time. For further improvement in knee joint condition, cartilage regeneration can be combined with HTO. Autologous chondrocyte implantation (ACI), osteochondral autologous transplantation (OAT), and microfracture have been known to be effective therapies for articular cartilage regeneration, but they are not suitable in case of osteoarthritis (OA) therapy. Recently, mesenchymal stem cells (MSCs) have been identified as a new option in the field of cartilage regeneration for the treatment of OA patients. The MSCs isolated from human umbilical cord blood (hUCB-MSCs) demonstrate higher proliferation and chondrogenic capacity than other MSCs. Reports on the clinical application of hUCB-MSCs are scarce, and there are no studies examining the use of hUCB-MSCs with concomitant HTO.

Research objectives

This study aimed to evaluate clinical outcomes and cartilage regeneration *via* second-look arthroscopy after implantation of hUCB-MSCs with concomitant HTO, for treatment of osteoarthritic knee with varus deformity.

Research methods

A total of 125 patients were included in this study with an average age of 58.3 ± 6.8 years (range: 43-74 years). All the patients had a varus deformity of more than 5° and a full-thickness International Cartilage Repair Society (ICRS) grade IV articular-cartilage lesion of more than 4 cm^2 in the medial compartment of the knee. All patients underwent second-look arthroscopy during hardware removal. Cartilage regeneration was evaluated macroscopically using the ICRS grading system in second-look arthroscopy. We also assessed the effects of patient characteristics, such as trochlear lesions, patient age, and lesion size, using the patients' medical records.

Research results

The results obtained in this study show that cartilage was regenerated to ICRS grade III or better in all the cases after implantation of hUCB-MSCs with concomitant HTO. Regenerated cartilage

in the ICRS grades I, II, and III groups improved the clinical outcomes of these patients. The ICRS grade I group showed the best clinical outcomes among the three groups. Indeed, all the scores in the ICRS grade I group improved over time compared with those of the ICRS grade II and III groups. Although some patients presented with partially regenerated cartilage, none of the patients showed lack of cartilage regeneration (ICRS grade IV).

Research conclusions

Our results show that implantation of hUCB-MSCs with concomitant HTO is an effective treatment option for patients with medial compartment osteoarthritis (MCOA). In addition, our results also suggest that the presence of trochlear or large cartilage lesions, or advanced age of the patient, does not significantly affect clinical outcomes in patients with MCOA undergoing HTO with hUCB-MSC implantation.

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