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ARTHROSCOPY AND SPORTS MEDICINE

Human umbilical cord blood-derived mesenchymal stem cell implantation for osteoarthritis of the knee

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Abstract

Introduction This study aimed to investigate the clinical outcomes after human umbilical cord blood-derived mesenchymal stem cell (hUCB-MSC) implantation for medial compartment (MC) osteoarthritis of the knee.

Materials and methods Inclusion criteria were patients older than 60 years, with a kissing lesion of the MC, a full-thickness chondral defect ≥ 4 cm^2 of the medial femoral condyle (MFC), and a varus deformity ≥ 3° on a long cassette scanogram. The mean age was 64.9 ± 4.4 years and the mean chondral defect of the MFC was 7.2 ± 1.9 cm^2. A mixture of sodium hyaluronate and hUCB-MSC was implanted into the chondral defect and a high tibial osteotomy was performed in all patients. International Knee Documentation Committee (IKDC), visual analog scale (VAS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were evaluated preoperatively and 1 year and 2 years postoperatively. Cartilage regeneration was evaluated in 14 (56%) patients by second-look arthroscopy at 1 year postoperatively.

Results Twenty-five patients underwent hUBC-MSC implantation. IKDC, VAS, and WOMAC scores at 1 year and 2 years improved significantly compared to preoperative scores. These scores at 1 year and 2 years were not significantly different between the body mass index (BMI) < 25 group and BMI ≥ 25 group. However, the < 65-year-old group showed superior IKDC scores at 1 year and 2 years and VAS score at 2 years than the ≥ 65-year-old group. Younger age and larger size of the chondral defect were associated with a significantly greater improvement in IKDC, VAS and WOMAC scores at 2 years. Second-look arthroscopy demonstrated International Cartilage Repair Society-Cartilage Repair Assessment grade I in six (42.9%) patients and grade II in eight (57.1%).

Conclusions hUCB-MSC implantation regenerated cartilage satisfactorily and showed satisfactory clinical outcomes in patients older than 60 years who had MC osteoarthritis.

Keywords Mesenchymal stem cell · Osteroarthritis · Second-look arthroscopy · Umbilical cord blood

Introduction

The incidence of osteoarthritis increases with age, and it is one of the most prevalent diseases in older people [1]. In the United States alone, 10% of men and 13% of women aged 60 years and older have been diagnosed with knee osteoarthritis [2]. Treatment of older patients with osteoarthritis traditionally consists of medication, osteotomy, or joint replacement. For disabling and advanced osteoarthritis of the knee with varus deformity, total knee arthroplasty has been a standard treatment. However, a previous study reported that the rate of sports participation actually decreased after knee arthroplasty, even if surgery improved the patients' activity levels and functional outcomes [3]. With the aging population, an increasing number of patients wish to remain active and are less willing to accept the limitations associated with non-operative treatment or joint replacement [4]. Therefore, cartilage repair procedures with an unloading procedure can be an alternative treatment for osteoarthritis of the knee with varus deformity in patients older than 60 years.

Since the 1980s, cell-based therapy has been applied for cartilage repair and has been rapidly developed over the past 30 years [5]. Clinical outcomes of autologous chondrocyte implantation (ACI) have been well documented in full-thickness chondral defect repair. ACI is indicated to

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localized chondral defects surrounded by healthy cartilage [6]. Therefore, ACI is usually not indicated to generalized osteoarthritis [7], and age 45 is a common insurance limit of ACI in the United States [4].

Mesenchymal stem cell (MSC) treatment may be an alternative option for bone, cartilage, tendon, and ligament regeneration [8, 9]. MSC can be easily collected from the bone marrow, adipose tissue, and synovial membrane [6]. MSC can be isolated from umbilical cord blood, although it was present in much lower numbers compared with bone marrow, adipose tissue, and other sources [10]. Unlike the bone marrow-, synovial- and adipose-derived MSCs, human umbilical cord blood-derived MSCs (hUCB-MSCs) have several advantages: they can be easily harvested from discarded umbilical cords obtained at birth, they exhibit high proliferation rates, they can be expanded for many population doublings, and they are hypo-immunogenic and non-tumorigenic [8]. However, clinical outcomes after hUCB-MSC implantation for the chondral defect of the knee have been reported rarely [11, 12]. We hypothesized that hUCB-MSC implantation demonstrates satisfactory clinical outcomes for patients older than 60 years who had medial compartment osteoarthritis of the knee. Therefore, the purpose of this retrospective study was to investigate the clinical outcomes after hUCB-MSC implantation for patients older than 60 years who had medial compartment osteoarthritis of the knee.

Materials and methods

Patient selection

This study retrospectively evaluated 41 patients who underwent hUCB-MSC implantation between April and December 2014. Inclusion criteria were patients older than 60 years with a kissing lesion of the medial compartment of the knee, a full-thickness chondral defect ≥ 4 cm^2 of the medial femoral condyle (MFC), and a varus deformity $\geq 3°$ on a long cassette scanogram. Exclusion criteria were patients younger than 60 years, with a full-thickness chondral defect < 4 cm^2 in the MFC or with equal to or less than grade III lesion of the MFC or the medial tibial plateau (MTP) based on Outerbridge classification. Patients with a varus deformity $< 3°$ were excluded, although they had a full-thickness chondral defect ≥ 4 cm^2. Sixteen patients were excluded. Finally, 25 patients were enrolled in this study. There were 23 (92%) women and 2 (8%) men with a mean age of 64.9 ± 4.4 (range 60–76) years.

Preparation of therapeutic mesenchymal stem cells

Human umbilical cord blood (UCB) was collected from umbilical veins after neonatal delivery, with informed consent from pregnant mothers. The UCB was isolated by separating mononuclear cells (MNCs) with Ficoll-Hypaque solution ($d = 1.077$ g/cm^3; Sigma-Aldrich, St. Louis, MO, USA). The separated MNCs were washed and suspended in minimum essential medium alpha (Gibco/Invitrogen, Carlsbad, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Gibco). Cultures were maintained at 37 °C in a humidified atmosphere containing 5% CO_2, wherein the culture medium was changed twice a week. Cells were verified for positive (CD29, CD73, CD90, CD105, CD166) and negative (CD14, CD45) surface markers by flow cytometry. Human UCB-MSCs were provided by MEDIPOST Co., Ltd. (Seongnam, Korea).

hUCB-MSCs at passage 6 were used as a stem cell drug (CARTISTEM, MEDIPOST) mixed with sodium hyaluronate (HA). Therapeutic use of CARTISTEM for cartilage repair was approved by the Korea Food and Drug Administration in January 2012. Before implantation, hUCB-MSC and HA were mixed according to the manufacturer's instructions. The therapeutic dosage of CARTISTEM was 500 µl/cm^2 of the defect area with a cell concentration of 0.5×10^7 cells per milliliter. Three types of stem cells were used for the patients enrolled in this study.

Surgical technique and postoperative rehabilitation

Standard anteromedial and anterolateral portals were created. Meniscectomy, meniscal repair, and lateral retinacular release were performed if necessary. A 4-cm longitudinal arthrotomy was performed 5 mm medial to the patella. For the chondral defect of the MFC, damaged cartilage was completely removed and the size of the defect was measured. Any sclerotic subchondral bone was removed using a burr. Multiple holes of 4-mm diameter and 4-mm length were created approximately 2 mm apart from the other holes using a CARTISTEM (MEDIPOST) drill bit. Then, a mixture of HA and hUCB-MSCs was implanted into the holes and trimmed to the height of the surrounding cartilage (Figs. 1, 2). For the defect of the MTP where drilling was possible, the same procedure was performed, but when drilling was impossible, microfracture was performed in the conventional way. The arthrotomy site was closed 5 min after implantation.

High tibial osteotomy (HTO) was performed conventionally. The correction angle was measured preoperatively according to the Miniaci method [13]. The osteotomy was fixed securely using either the TOMOFIX (DePuySynthes,

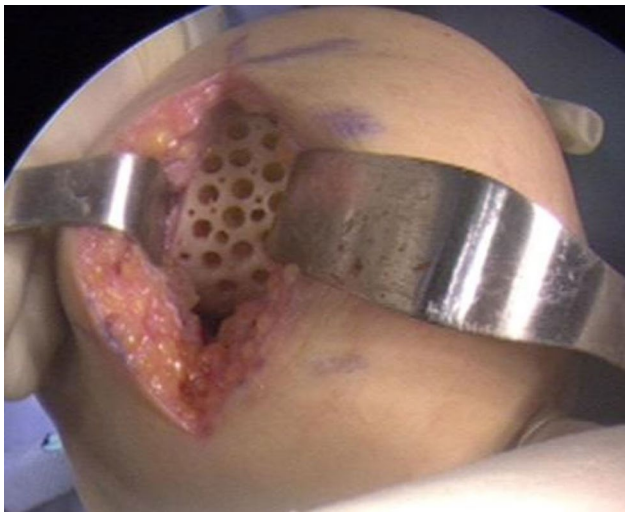

Fig. 1 Damaged cartilage and sclerotic subchondral bone were removed and multiple holes were created in the left knee of a 67-year-old woman

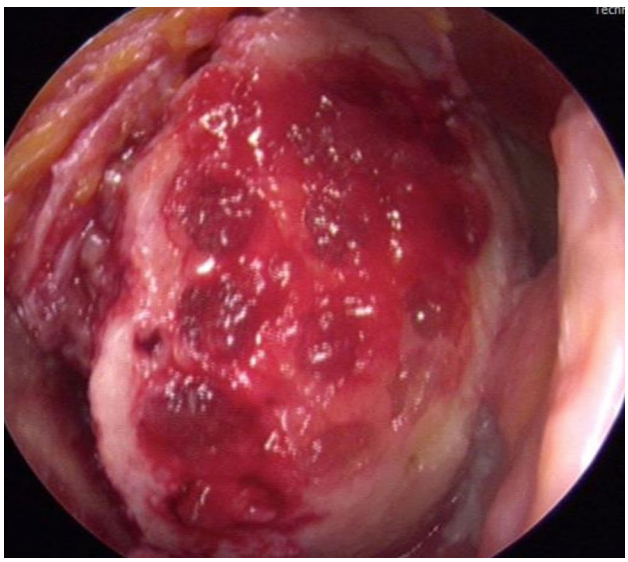

Fig. 2 In same patient, a mixture of HA and hUCB-MSC was implanted into the holes and trimmed to the height of the surrounding cartilage

Solothurn, Switzerland) or OHTOFIX (Ohto Medical, Gyeonggido, Korea) plate. Correction of the varus deformity was confirmed using fluoroscopy, and the weight-bearing line (WBL) was aligned to the lateral tibial eminence. TOMOFIX was used in 12 patients and OHTOFIX was used in 13 patients.

After surgery, non-weight bearing with brace was recommended for 8 weeks. Range of motion exercises with a continuous passive motion machine, quadriceps-strengthening exercise, and ankle pump were initiated the day after surgery. Physiotherapy was performed 2 or 3 times per week for 4 weeks after surgery. All patients underwent progressive and comprehensive rehabilitation for 3 months to increase ROM and muscle power. Full weight bearing was allowed 12 weeks after surgery.

Outcome evaluation and second-look arthroscopy

The size of the chondral defect of the MFC and MTP were measured during surgery and their sum was calculated. The International Knee Documentation Committee (IKDC), visual analog scale (VAS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were evaluated preoperatively and at 1 year and 2 years postoperatively. Patients were divided into the <65-year-old group and ≥ 65-year-old group. Patients were also divided based on their body mass index (BMI) into the "not obese" group with BMI <25 and "obese" group with BMI ≥ 25.

Of the 25 patients, 14 (56%) patients underwent second-look arthroscopy at 1 year after surgery. Cartilage regeneration was evaluated according to the International Cartilage Repair Society-Cartilage Repair Assessment (ICRS-CRA) [14]. The CRA evaluates three items, namely, degree of defect repair, integration to border zone, and macroscopic appearance, and graded as follows: normal as grade I, nearly normal as grade II, abnormal as grade III, and severely abnormal as grade IV. ICRS grade was determined based on the agreement of two from three orthopedic surgeons.

Statistical analysis

In this study, independent variables were age, BMI, and total size of the chondral defect, and dependent variables were IKDC, VAS, and WOMAC scores. All values were described as mean $\pm$ standard deviation. The Wilcoxon signed-rank test was performed to compare the IKDC, VAS, and WOMAC scores between preoperative and postoperative 1 year and 2 years for all patients. Mann–Whitney test was used to compare dependent variables between two groups according to age and BMI. The association between dependent variables and independent variables was analyzed by linear regression. All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Corp., Armonk, NY). $p<0.05$ was considered to be statistically significant.

Results

Clinical outcomes and second-look arthroscopy results

The mean follow-up period was 26.7 ± 1.8 (range 24–31) months. The mean BMI was 24.9 ± 3.1 kg/m^2 (range

19.2–34.2 kg/m^2), and the mean WBL was 8 ± 13.1% (range − 20–28.6%). The mean sizes of the MFC and MTP chondral defects were 7.2 ± 1.9 cm^2 (range 4.2–12.8 cm^2) and 2.2 ± 1.1 cm^2 (range 0.2–6.1 cm^2), respectively. The total mean size of the defect was 9.4 ± 3.1 cm^2 (range 5.3–18.9 cm^2). IKDC, VAS, and WOMAC scores at 1 year and 2 years after surgery improved significantly compared to their corresponding preoperative scores ($p = 0.000$). Those scores at 2 years after surgery improved significantly than those at 1 year ($p = 0.005$, $p = 0.03$, and $p = 0.007$, respectively) (Table 1). IKDC, VAS, and WOMAC scores at 1 year and 2 years after surgery were not significantly different between the "not obese" and "obese" groups ($p > 0.05$) (Table 2). However, the < 65-year-old group showed superior IKDC scores at 1 year and 2 years and VAS score at 2 years after surgery than the ≥ 65-year-old group. VAS scores at 1 year after surgery and WOMAC scores at 1 year and 2 years after surgery did not differ between < 65-year-old group and ≥ 65-year-old group ($p > 0.05$) (Table 3). Younger age and larger size of the chondral defect were associated with significantly greater improvements in the IKDC, VAS, and WOMAC scores at 2 years on linear regression analysis.

Of 25 patients, 14 (56%) underwent second-look arthroscopy 1 year after surgery. Among them, HTO plate and screws were removed from 12 patients, and hUCB-MSC implantation was performed for the opposite knee in two patients. Second-look arthroscopy demonstrated ICRS grade I in six (42.9%) patients and grade II in eight (57.1%) (Fig. 3). The Mann–Whitney test showed that the mean VAS scores at 1 year after surgery in grade I group and grade II groups on the second-look arthroscopy were 8.3 ± 9.8 and 28.8 ± 16.4, respectively ($p = 0.020$). However, other clinical

Table 1 Pre-operative and follow-up clinical scores

	Pre-operative	At 1 year	At 2 year	*p* value[†]	*p* value[‡]	*p* value[#]
IKDC score	24.3 ± 11.1	58.9 ± 10.3	68.5 ± 12.7	0.000	0.000	0.005
VAS score	76.4 ± 16.6	20.4 ± 15.1	12.8 ± 11.7	0.000	0.000	0.030
WOMAC score	57.3 ± 11.4	15.6 ± 9.6	10.2 ± 7.9	0.000	0.000	0.007

IKDC International Knee Documentation Committee, *VAS* visual analog scale

WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

[†]*p* value stands for p value of pre-operative score vs. score at 1 year after surgery

[‡]*p* value stands for p value of pre-operative score vs. score at 2 years after surgery

[#]*p* value stands for p value of score at 1 year after surgery vs. score at 2 years after surgery

Table 2 Comparison of clinical scores between BMI < 25 and BMI ≥ 25 groups

	BMI < 25 (*n* = 11)	BMI ≥ 25 (*n* = 14)	*p* value
IKDC score at 1 year	60.2 ± 12.1	58.0 ± 8.9	0.649
IKDC score at 2 years	65.7 ± 13.5	70.7 ± 12.4	0.361
VAS score at 1 year	19.1 ± 17.0	21.4 ± 14.1	0.424
VAS score at 2 years	15.5 ± 10.4	10.7 ± 12.7	0.252
WOMAC score at 1 year	16.2 ± 10.1	15.1 ± 9.6	0.691
WOMAC score at 2 years	11.8 ± 7.8	8.9 ± 8.0	0.424

IKDC International Knee Documentation Committee, *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index, *BMI* body mass index

Table 3 Comparison of clinical scores between age < 65 and age ≥ 65 groups

	Age < 65 (*n*=13)	Age ≥ 65 (*n*=12)	*p* value
IKDC score at 1 year*	63.3 ± 8.5	54.2 ± 10.1	0.026*
IKDC score at 2 years*	73.9 ± 10.9	62.6 ± 12.6	0.03*
VAS score at 1 year*	17.7 ± 13.6	23.3 ±16.7	0.503
VAS score at 2 years*	8.5 ± 11.4	17.5 ± 10.6	0.035*
WOMAC score at 1 year*	12.4 ± 7.9	19.0 ± 10.4	0.137
WOMAC score at 2 years*	6.5 ± 6.5	14.2 ± 7.5	0.106

IKDC International Knee Documentation Committee, *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

*Statistically significant

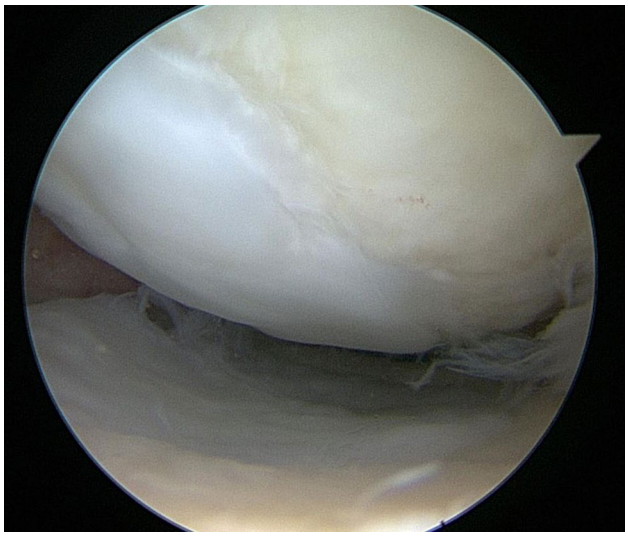

Fig. 3 In same patient, second-look arthroscopy demonstrated a satisfactorily covered cartilage on the previous chondral defect on the medial femoral condyle

scores did not differ between the grade I and II groups. No persistent effusion, synovitis, localized eruption, or localized erythema that was considered as allergic reaction after hUCB-MSC implantation was noted. There was no infection, neurovascular injury, deep vein thrombosis, or non-union associated with HTO.

Discussion

This study demonstrated that clinical scores improved over time. Clinical scores at 2 years after surgery improved significantly compared to those at 1 year regardless of obesity. Both the "not obese" and "obese" groups showed improvements in clinical scores over time, and both groups showed no significant difference in clinical scores (Table 3). However, age was an important factor affecting clinical outcomes. The < 65-year-old group showed superior IKDC scores at 1 year and 2 years and VAS scores at 2 years than the ≥ 65-year-old group. Moreover, younger age was associated with a significantly greater improvement of IKDC, VAS, and WOMAC scores at 2 years. However, clinical scores of ≥ 65-year-old group improved over time. The size of the chondral defect was another factor affecting clinical outcomes, but it did not correlate with the IKDC, VAS, and WOMAC scores at 1 year and 2 years. However, increasing size and age were associated with improved clinical scores at 2 years.

This study demonstrated satisfactory restoration of chondral defects in patients who underwent second-look arthroscopy. This outcome was a promising result for cartilage repair of patients older than 60 years, because there are concerns over the efficacy of cartilage repair procedures in older patients [4]. In a degenerative microenvironment, the implanted chondrocytes may undergo undesired dedifferentiation or apoptosis [15, 16]. In older patients, metabolic cell activity is assumed to be lower [4]. Therefore, cartilage repair using autologous chondrocyte has been performed rarely in older patients [12]. Rosenberger et al. tried the ACI for 56 patients with a mean age of 48.6 years (range 45–60 years) and followed them for mean 4.7 years. Twenty-eight (50%) patients underwent concomitant osteotomies to correct malalignment. At the latest available follow-up, 72% of patients rated good or excellent results. However, additional arthroscopic procedures were required in 24 (43%) patients, and there were 8 (14%) failures. They concluded that a failure rate of ACI in older patients was comparable with rates reported in younger patients [4].

MSC treatment may represent an alternative option for cartilage regeneration [8]. A recent meta-analysis demonstrated that MSC treatment for knee osteoarthritis could significantly decrease VAS scores and increase IKDC scores at the 24-month follow-up compared with controls. MSC therapy also showed significant decreases in WOMAC score after the 12-month follow-up, and side effects showed no statistical difference between the MSC treatment group and the control group [17]. Most investigators used cultured MSCs from the bone marrow and injected MSCs arthroscopically rather than implantation [18–21]. However, like chondrocytes, MSC properties also change with age. MSC density in bone marrow decreases and aged MSCs are slower to proliferate [22].

Treatment of osteoarthritis of the knee with hyaluronic acid and mesenchymal stem cells is rarely reported. Gobbi et al. treated 23 patients with full-thickness chondral injury using hyaluronic acid-based scaffold embedded with bone marrow aspirate concentrate. At mean 8 years follow-up after surgery, median Tegner, visual analog scale, and IKDC subjective scores were 4, 0.3, and 85, respectively. Median KOOS Pain, Symptom, and Activities of Daily Living were 94, 89, and 99, respectively. There was a negative correlation between patient age and final outcome scores of the IKDC, Tegner, and KOOS subsets of Pain, Activities of Daily Living, and Sports/Recreation [23]. Lamo-Espinosa et al. reported a short-term outcome after intra-articular injection of autologous bone marrow mesenchymal stem cells (BM-MSCs) with hyaluronic acid for the treatment of knee osteoarthritis. At 12 months, WOMAC score was 16.5 and VAS score was 2. Radiographs showed no narrowing of the knee joint space and MRI showed that joint damage decreased slightly. They concluded that the single intra-articular injection of in vitro expanded BM-MSCs together with HA is a safe and feasible procedure that results in a clinical and functional improvement of knee OA, especially

when 100×10^6 cells are administered [24]. Wong et al. compared intra-articular injection of MSCs with hyaluronic acid group and injection of isolated hyaluronic acid group. All patients underwent HTO and microfracture. MSCs with hyaluronic acid group showed significantly better scores. The effect of treatment showed an added improvement of 7.6 for IKDC scores, 7.6 for Lysholm scores, and 0.6 for Tegner scores. MRI scans performed 1 year after surgery showed significantly better MOCART scores in MSCs with hyaluronic acid group than isolated hyaluronic acid group [25].

Collection of MSCs from the bone marrow is a difficult and invasive procedure. However, hUCB-MSC can be obtained easily from the umbilical cord discarded at birth and is another source for cartilage repair. It may have higher expansion potential than MSCs isolated from other tissues [10]. In vivo studies of hUCB-MSC implantation have been rarely reported in the literature. In an animal study using minipigs, Ha et al. tested the cartilage reparative effect of a mixture of three hUCB-MSC cell lines with 4% HA. They created a full-thickness chondral injury in the trochlea of each knee in six minipigs. Three weeks later, an osteochondral defect, 5 mm wide by 10 mm deep, was created, followed by an 8-mm-wide and 5-mm-deep reaming. A mixture (1.5 ml) of hUCB-MSCs (0.5×10^7 cells per milliliter) and 4% HA hydrogel composite was implanted into the defect on the right knee. The osteochondral defect created in the same manner on the left knee was untreated to act as the control. At 12 weeks postoperatively, the pigs were sacrificed, and the degree of subsequent cartilage regeneration was evaluated by gross and histological analyses. The transplanted knee demonstrated superior and more complete hyaline cartilage regeneration compared with the control knee [26].

Clinical outcomes after hUCB-MSC implantation for chondral defect in the human knee have been reported rarely. Park et al. [11] reported successful restoration of a large osteochondral defect on the lateral femoral condyle in a 31-year-old woman using CARTISTEM. They used CARTISTEM for ICRS grade IV lesions in seven patients in another case series. Their mean age was 58.7 years (range 29–77 years). The 12-week second-look arthroscopy demonstrated matured repair tissue. The VAS and IKDC scores were improved at 24 weeks. The improved clinical outcomes were maintained over 7 years after surgery. The histological findings at 1 year showed hyaline-like cartilage. Magnetic resonance imaging at 3 years showed regenerated cartilage [12]. Compared to the above two reports, this present study enrolled 25 patients older than 60 years who had osteoarthritis rather than isolated condylar defect of the knee. Therefore, the present study is the first case series reporting clinical and arthroscopic findings after hUCB-MSC implantation for patients older than 60 years with osteoarthritis.

This study had several limitations. First, there was no control group. Patients who underwent microfracture combined with HTO may be a control group. Further study is needed to investigate the superiority of repaired cartilage in patients who underwent hUBC-MSC implantation than that of the control group. However, the inferior result of the microfracture in patients older than 40 years than in of patients younger than 40 years is well known in the literature. Therefore, augmentation of the microfracture procedure is necessary to obtain satisfactory clinical outcomes in patients older than 60 years with osteoarthritis. Second, a small number of patients was enrolled in this study. Third, the follow-up period was too short to evaluate clinical outcomes of the osteoarthritic knees. Longer follow-up is needed to demonstrate the safety of hUBC-MSC implantation in the human knee and durability of the regenerated cartilage. However, all patients were followed for more than 24 months. Fourth, clinical outcomes would be more affected by HTO than by hUBC-MSC implantation. Recent two studies focused cartilage regeneration of the medial compartment after HTO without cartilage procedure. Jung et al. performed second-look arthroscopy at 2 years after HTO to evaluate regeneration of the articular cartilage of the medial compartment. They found that the fibrocartilage was regenerated on previous lesion of the medial femoral condyle in 92% of knees. However, even regeneration of fibrocartilage was found only 4% of knees [27]. Kim et al. also performed second-look arthroscopy at 2 years after HTO. They found that the lesions in the medial femoral condyle improved in 51.9% of knees and 45.2% knees showed no change of the articular cartilage status [28]. Although isolated HTO can regenerate fibrocartilage, healing response would be limited and durability of repaired tissue is a big concern. Further study of hUBC-MSC implantation for patients with normal limb alignment is needed to demonstrate the efficacy of cartilage restoration for patients older than 60 years. Fifth, only 14 (56%) of 25 patients underwent second-look arthroscopy. Result from other 11 patients who did not undergo second-look arthroscopy would affect final outcomes of the ICRS grade of the repaired cartilage. Removal of the plate and arthroscopy are another burdens to older patients. Sixth, second-look findings were not correlated with clinical scores, because the second-look arthroscopy was performed at 1 year after surgery and clinical scores were evaluated at 1 year and 2 years after surgery.

Conclusion

hUCB-MSC implantation with HTO regenerated cartilage satisfactorily and showed satisfactory clinical outcomes in patients older than 60 years who had medial compartment osteoarthritis.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This study was reviewed and approved by the institutional review board of the Korea Ministry of Health and Welfare.

Informed consent All patients signed an informed consent form.

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