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Allogenic umbilical cord blood-derived mesenchymal stromal cell implantation was superior to bone marrow aspirate concentrate augmentation for cartilage regeneration despite similar clinical outcomes

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Abstract

Purpose The aim of this study was to compare clinical and second-look arthroscopic outcomes between bone marrow aspirate concentrate (BMAC) augmentation and human umbilical cord blood-derived mesenchymal stromal cell (hUCB-MSC) implantation in high tibial osteotomy (HTO) for medial compartmental knee osteoarthritis and identify the relationship between articular cartilage regeneration and HTO outcomes.

Methods A total of 176 patients who underwent HTO combined with a BMAC or hUCB-MSC procedure for medial compartment osteoarthritis (Kellgren–Lawrence grade 3) between June 2014 and September 2018 with a minimum follow-up of 2 years were reviewed. After HTO, multiple holes were drilled at cartilage defect sites of the medial femoral condyle (MFC), and then prepared BMAC or hUCB-MSCs in combination with scaffolds were implanted in the MFC lesions. After propensity score matching based on sex, age, body mass index, and lesion size, 55 patients in each of the BMAC and hUCB-MSC groups were successfully matched. Second-look arthroscopic findings were assessed according to the International Cartilage Repair Society (ICRS) Cartilage Repair Assessment (CRA) grading system and Koshino staging system. Clinical outcomes were evaluated using the International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Short-Form 36 (SF-36), and Tegner activity scores.

Results At a mean follow-up of 33 months, clinical outcomes including IKDC, KOOS, SF-36, and Tegner activity scores were significantly improved in both groups ($p < 0.001$); however, there were no differences between the two groups. Second-look arthroscopy showed better healing of regenerated cartilage in the hUCB-MSC group (Grade I [4 cases, 9.1%]; Grade II [30 cases, 68.2%]; Grade III [11 cases, 22.7%]) than in the BMAC group (Grade I [1 case, 2.7%]; Grade II [20 cases, 54.1%]; Grade III [11 cases, 29.7%]; Grade IV [5 cases, 13.5%]) according to the ICRS CRA grading system ($p = 0.040$). There was no significant intergroup difference in terms of defect coverage based on the Koshino staging system ($p = 0.057$). Moreover, ICRS CRA grades at second-look arthroscopy were significantly correlated with clinical outcomes ($r = -0.337$; $p = 0.002$).

Conclusion There were no significant differences in the clinical outcomes between the two groups. 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.

Keywords hUCB-MSC · BMAC · Cartilage regeneration · Clinical outcomes · High tibial osteotomy · Second-look arthroscopy

Introduction

High tibial osteotomy (HTO) is a reliable treatment solution for the management of medial compartment osteoarthritis of the knee with varus deformity in younger and/or physically active patients [1, 2]. This procedure alters the weight-bearing axis, decreasing load on the weight-bearing medial

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compartment, and allowing healing of the cartilage by altering forces on it [27, 40, 52]. Several studies have reported articular cartilage regeneration along with improved outcomes after HTO [17, 25–27, 35].

HTO improves the status of articular cartilage by providing an ideal mechanical environment; however, it is limited by the preferential formation of fibrocartilage, which has insufficient biomechanical and biochemical properties compared to those of the native hyaline cartilage [27, 35, 51]. Moreover, outcomes after HTO deteriorate over time, and correction of malalignment alone results in partial remodeling of the cartilage [40, 42]. Thus, the overall long-term efficacy of HTO is controversial. To overcome these limitations, HTO and additional cartilage regenerative procedures are increasingly being combined to improve articular cartilage regeneration and surgical outcomes [14, 23, 40, 45, 52]. With recent investigations into cartilage regeneration, implantation of mesenchymal stromal cells (MSCs) has been suggested as a useful biological tool for managing degenerated cartilage because MSCs have chondrogenic and paracrine signaling potential [8, 20, 21, 32, 34, 43, 49, 50]. Many human tissues, including the bone marrow, adipose tissue, umbilical cord blood, and synovium, are well-known sources of adult MSCs [12].

The combination of HTO and cartilage repair procedures has been broadly utilized for articular cartilage regeneration and alignment correction [8, 24, 31, 32, 34]. One such procedure, autologous bone marrow aspirate concentrate (BMAC) augmentation, seems to enhance cartilage regeneration quality and achieve better clinical outcomes than other sources after HTO [8, 19–21, 24]. BMAC augmentation depends on the inclusion of multipotent stromal cells and a number of growth factors that stimulate MSC differentiation into chondrocytes, which potentially results in the production of native, hyaline-like cartilage [3, 48]. Human umbilical cord blood-derived MSCs (hUCB-MSCs) have also increasingly become a focal point of research because of their advantages over other autologous stromal cells, such as their noninvasive harvesting procedure, low immunogenicity, low donor-site morbidity, and good expansion capacity [16, 28]. Recent studies have shown promising results for hUCB-MSC implantation in knee osteoarthritis [10, 43, 49, 50].

However, there appear to be no previous reports comparing the outcomes of these two cartilage augmentation procedures in patients who have undergone medial opening wedge HTO (MOHTO) for knee osteoarthritis. Therefore, the aim of this study was to compare the clinical and radiographic outcomes as well as the second-look arthroscopic outcomes after HTO coupled with BMAC and hUCB-MSC treatments and to determine the relationship between articular cartilage regeneration and postoperative outcomes after HTO. The hypothesis of this study was that HTO coupled with hUCB-MSC implantation would demonstrate better clinical outcomes and superior articular cartilage regeneration than HTO coupled with BMAC augmentation based on second-look arthroscopy.

Materials and methods

Patients

This study was approved by the relevant institutional review board. Between June 2014 and September 2018, 229 MOHTOs for medial compartment osteoarthritis were performed an academic medical center in Korea by two experienced orthopedic surgeons using the same techniques. Preoperatively, all patients were routinely recommended to undergo second-look arthroscopy at the time of plate removal by explaining its purpose—to assess the medial compartmental osteoarthritis lesion and need for additional arthroscopic procedures. MOHTO was indicated for patients aged ≥ 40 years who had isolated medial compartment osteoarthritis and varus tibiofemoral alignment without functional instability of the anterior cruciate ligament. At the time of preoperative examinations, the patient was informed about the two cartilage regeneration methods, following which they chose either the BMAC or hUCB-MSC procedure after weighing the advantages and shortcomings of the treatments.

Patients who underwent MOHTO combined with the BMAC or allogenic hUCB-MSC procedure for Kellgren–Lawrence grade 3 knee osteoarthritis and medial femoral condyle (MFC) full-thickness cartilage defects (≥ International Cartilage Repair Society [ICRS] grade 3 lesions) [7] were included.

Patients with knee range of motion < 100° with flexion contracture > 15°, presence of ICRS grade > 2 cartilage lesions affecting the lateral and patellofemoral compartments, anterior or posterior cruciate ligament insufficiency, traumatic knee arthritis or inflammatory arthritis, and follow-up periods < 2 years were excluded.

Of the 176 eligible patients (176 knees), 110 patients with a mean follow-up of 33.0 months (range, 24.0–52.1 months) were included after propensity score (PS) matching based on sex, age, body mass index (BMI), and the MFC defect size (Fig. 1).

Preparation of MSCs

BMAC

Under spinal anesthesia, bone marrow was aspirated from the contralateral anterior superior iliac spine. A 60 mL heparinized syringe was used, and at least 40 mL of bone marrow was collected. The bone marrow was transferred to a 50 mL sterilized tube and centrifuged for 4 min at

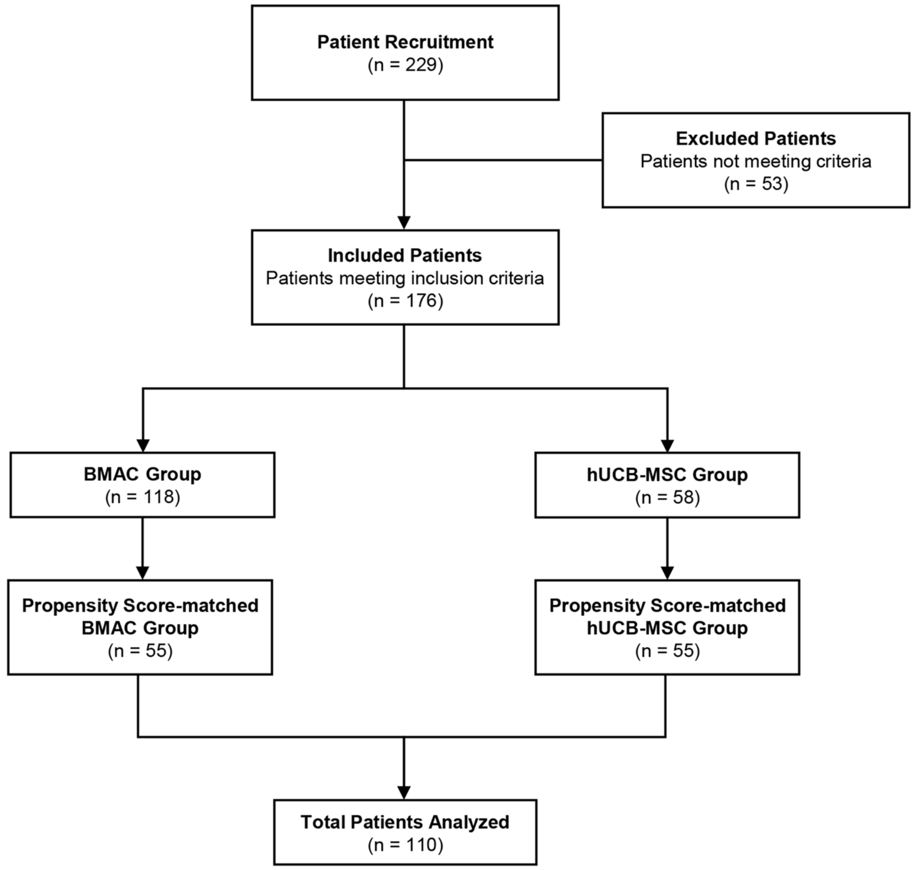

Fig. 1 Flow diagram describing patient enrollment process. BMAC, bone marrow aspirate concentrate; hUCB-MSC, human umbilical cord blood-derived mesenchymal stromal cell

2500 rpm to concentrate the bone marrow cells. The concentrated bone marrow was collected with a new 60 mL heparinized syringe, which theoretically contained the accumulated MSCs [11].

hUCB-MSCs

A medicinal product (Cartistem, a composite of hUCB-MSCs and hyaluronic acid (HA) hydrogel) produced according to regulatory authority and Good Manufacturing Practice guidelines was provided as a new investigational drug by Medipost (Seoul, South Korea). Therapeutic use of Cartistem for cartilage repair was reviewed and approved by the Korea Food and Drug Administration in January 2012 [43]. This product consists of 1.5 mL of cord blood-derived MSCs (7.5×10^6) and 4% HA. hUCB-MSCs and HA were mixed according to the manufacturer's instructions prior to application during surgery. The defect area was assessed by magnetic resonance imaging prior to surgery, and hUCB-MSCs were administered at a therapeutic dose of 500 mL/cm^2 of defect with a cell concentration of 0.5×10^7 cells/mL [18, 49].

Surgical techniques and postoperative management

Templating was conducted with a standing whole lower extremity radiograph preoperatively and performed according to the method of Dugdale et al. to determine the extent of necessary correction [13]. The goal of HTO was to shift the weight-bearing line by 62.5% of the tibial plateau width, measured from the medial tibial plateau edge (Fujisawa point), to achieve a postoperative mechanical valgus angle of 3°–5° [17].

Arthroscopic examinations were performed on a routine basis before HTO. All detected cartilage injuries were categorized according to ICRS classification. Arthroscopic procedures, including debridement or meniscectomy, were performed to treat meniscal problems based on the surgeon's judgment. Biplanar MOHTO was performed according to the AO international knee expert group using a locking wedge plate [30, 38]. Osteotomy opening and adequate correction were assessed by placing a long alignment rod on the extended knee from the center of the hip joint to the center of the ankle joint; whether it passed through a point located 62.5% lateral to the medial cortex of the tibial plateau was assessed under fluoroscopic guidance. A cancellous bone allograft was performed only in some cases, as determined intraoperatively by the surgeons.

After HTO, a mini-arthrotomy was performed to access the MFC. In the BMAC group, cartilage defects were prepared and debrided down to the bed using curettes until healthy-looking underlying bone was visible. A microfracture procedure was then performed by drilling multiple holes, and the prepared BMAC immersed in the fibrin sealant patch (TachoSil; Takeda Pharma A/S, Linz, Austria) was implanted onto the cartilage defects and secured to the surrounding cartilage with fibrin glue (Greenplast kit®; Green Cross, Seoul, Korea). In the hUCB-MSC group, cartilage defects were debrided in the same manner as described for the BMAC group. Multiple drill holes, approximately 4 mm deep and 4 mm in diameter, were created with a drill bit (Medipost) at cartilage defect sites of the MFC. The main holes were approximately 3 mm apart with a ridge of bone remaining, and smaller holes 2 mm in diameter were subsequently made in the space between them. The hUCB-MSC and HA hydrogel composite was then implanted into the drill holes in the cartilage defects from the base to the surface [10, 43, 49].

Low molecular weight heparin and venous impulse foot pumps were routinely prescribed as prophylaxis for deep vein thrombosis. The same rehabilitation protocol was used for both groups. On the first postoperative day, quadriceps strengthening exercises and ankle movement were initiated. With the use of a continuous passive motion machine, passive range-of-motion exercises were started on the second postoperative day, and active range of motion exercises were encouraged within a tolerable range. Patients were allowed to perform partial weight-bearing crutch ambulation after 6 weeks with a knee brace and full weight-bearing after 12 weeks. Second-look arthroscopy was performed along with plate removal. After confirmation of union at the osteotomy site by radiographs, secondary arthroscopic assessment was performed simultaneously with plate removal after a mean follow-up of 17.0 months (Figs. 2 and 3).

Clinical evaluation

The primary clinical outcome measure was the International Knee Documentation Committee (IKDC) questionnaire [47]. Secondary clinical outcome measures included the Knee Injury and Osteoarthritis Outcome Score (KOOS) [46], Short-Form (SF) 36 questionnaire [56], and Tegner activity score [53]. Clinical assessments were performed preoperatively and during follow-up by two independent observers blinded to the operative procedures and radiographic analysis.

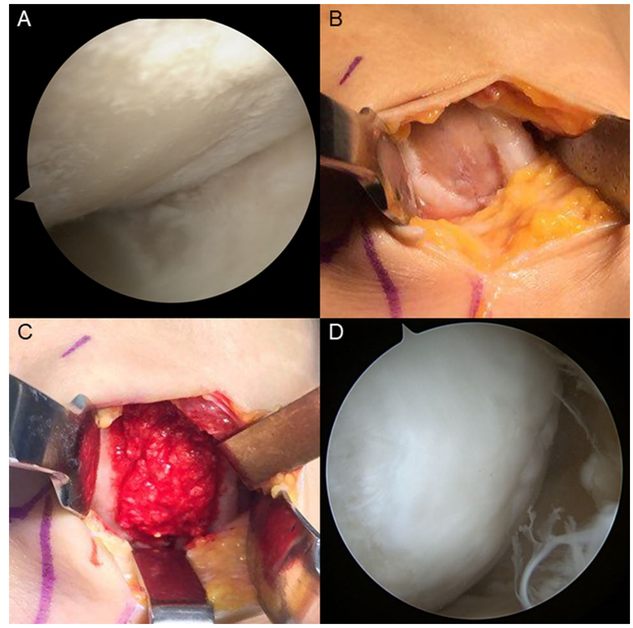

Fig. 2 A 54-years-old woman underwent HTO with BMAC augmentation procedure followed by second-look arthroscopy for plate removal after at least 1 postoperative year. **a** Arthroscopic image during osteotomy showing a cartilage defect of the medial femoral condyle. **b** Cartilage defects were prepared and debrided down to the bed using curettes until the healthy-looking underlying bone was visible. **c** After microfracture, the prepared BMAC immersed in the fibrin sealant patch was implanted onto the cartilage defects. **d** Second-look arthroscopic image at the time of plate removal performed 1.2 years postoperatively showing good coverage of the defect with smooth cartilage and complete integration (ICRS CRA grade I)

Radiographic evaluation

Standardized anteroposterior, lateral, and Merchant views of the knee and standing whole lower extremity radiographs were obtained preoperatively; at 1, 3, 6, and 12 months postoperatively; and annually thereafter. Radiographic evaluation included varus malalignment (mechanical hip–knee–ankle axis angle), posterior tibial slope, medial proximal tibial angle, and Kellgren–Lawrence grade.

Arthroscopic evaluation

The MFC articular cartilage was evaluated by arthroscopy before and approximately 1.4 years after HTO. The ICRS grading system was used to grade cartilage degeneration at initial HTO. In this grading system, superficial lesions, fissures, and cracks are considered grade 1 cartilage defects, and lesions extending down to < 50% of the cartilage depth are considered grade 2 defects. Grade 3 defects are defined as those extending down to > 50% of the cartilage depth but not involving the subchondral bone; those involving the subchondral bone are classified as grade 4.

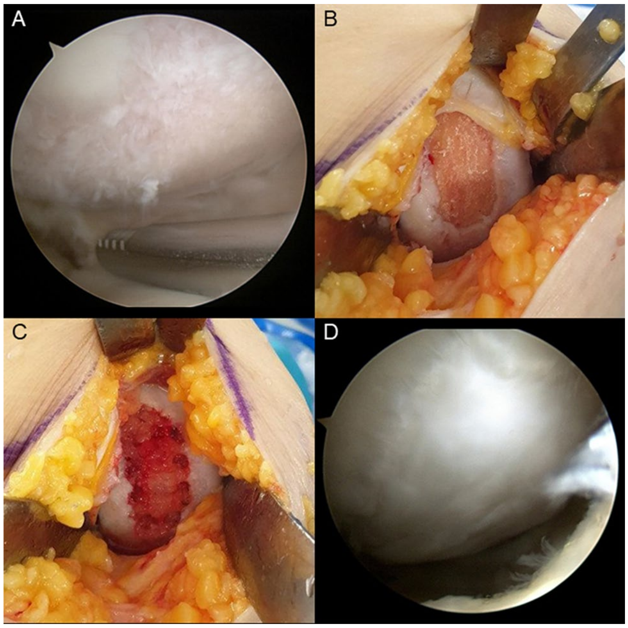

Fig. 3 A 52-year-old woman underwent HTO with hUCB-MSC implantation procedure followed by second-look arthroscopy for plate removal after at least 1 postoperative year. **a** Arthroscopic image during osteotomy showing a cartilage defect of the medial femoral condyle. **b** Cartilage defects were prepared and debrided down to the bed using curettes until the healthy-looking underlying bone was visible. **c** A hUCB-MSC and HA hydrogel composite was implanted into the drill holes in the cartilage defects from the base to the surface. **d** Second-look arthroscopic image at the time of plate removal performed 1.4 years postoperatively showing good coverage of the defect with smooth cartilage and complete integration (ICRS CRA grade I)

The Cartilage Repair Assessment (CRA) of the ICRS was used to evaluate the quality of articular cartilage regeneration during second-look arthroscopy (Table 1). In addition, the status of the regenerated cartilage was evaluated according to the macroscopic staging system described by Koshino et al. [35]—Grade A, no regenerative change; Grade B, pink fibrous tissue with or without partial coverage with white fibrocartilage, and Grade C, total cartilage regeneration. Radiographic and arthroscopic findings were evaluated based on a consensus between two independent observers who did not directly participate in the surgical procedures and were blinded to the study aim.

Statistical analysis

Differences in normally distributed variables were analyzed using paired and independent *t* tests. The Wilcoxon signed-rank test and Mann–Whitney *U* test were used to analyze differences when normality was absent. Spearman rank-correlation analysis was performed to evaluate associations between the ICRS CRA grade during second-look arthroscopy and clinical outcomes after HTO. The Chi-square test or Fisher's exact test was used to analyze differences in categorical variables. A p value < 0.05 was considered statistically significant.

Results

Patient demographics

After PS matching, 55 patients per group were matched for analysis. There were no significant differences in demographic characteristics or clinical data between the groups (Table 2).

Clinical outcomes

As shown in Table 3, all clinical scores (IKDC, KOOS, SF-36, and Tegner activity score) had improved over preoperative values at the latest follow-up in both groups ($p < 0.001$). However, there were no significant differences between the two groups (n.s.).

Radiologic outcomes and arthroscopic findings

Radiographic outcomes showed improved knee joint alignment over preoperative values at the latest follow-up (Table 4). However, there were no significant differences between the two groups (n.s.). Moreover, initial cartilage status findings were not significantly different between the two groups (n.s.).

After a mean follow-up of 17.0 months, 81 (73.6%) patients (37 in the BMAC group and 44 in the hUCB-MSC group) underwent second-look arthroscopy along with plate removal. Second-look arthroscopic findings related to articular cartilage regeneration according to the ICRS CRA grading system and Koshino staging system are summarized in Table 5. The hUCB-MSC group showed significantly better cartilage regeneration than the BMAC group based on the ICRS CRA grading system ($p = 0.040$). There was no significant intergroup difference in terms of defect coverage according to the Koshino staging system (n.s.).

The mean ICRS CRA scores at second-look arthroscopy were 9.2 ± 2.2 and 7.2 ± 3.0 in the hUCB-MSC ($n = 44$) and BMAC groups ($n = 37$), respectively. A significant correlation was demonstrated between the ICRS CRA grades on second-look arthroscopy and postoperative clinical outcomes ($r = -0.337$; $p = 0.002$). In other words, as the quality of articular cartilage regeneration increased, the IKDC scores increased significantly.

Table 1 International cartilage repair society cartilage repair assessment

	Points
Degree of defect infill	
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	11–8
Grade III: abnormal	7–4
Grade IV: severely abnormal	3–1

Postoperative complications and adverse events

No severe postoperative complications or adverse reactions were observed during the treatment or follow-up. One patient in the BMAC group complained of postoperative stiffness; the patient underwent manipulation under anesthesia 2 months postoperatively and achieved recovery without undergoing any further procedures.

Discussion

The principal finding of the present study was that clinical outcomes improved regardless of whether hUCB-MSCs or BMAC were administered. 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, the hUCB-MSC implantation procedure resulted in superior articular cartilage regeneration according to the ICRS CRA grades, which significantly correlated with clinical outcomes, compared to the BMAC augmentation procedure in patients undergoing HTO.

This study is the first to compare outcomes at least 2 years after HTO with two different cartilage regenerative methods, BMAC and hUCB-MSCs, for the treatment of medial compartment knee osteoarthritis. After matching the patient baseline characteristics, the study results can potentially provide the clinically significant information that hUCB-MSC implantation is more effective than BMAC augmentation for cartilage regeneration in the management of medial compartment osteoarthritis.

Numerous clinical studies have reported good short- to intermediate-term clinical outcomes after HTO [6, 36, 41, 57]. However, several studies have found deterioration of successful outcomes over time [2, 40, 42, 51], and greater attention has been recently directed at identifying whether inadequate articular cartilage regeneration is related to worse outcomes after HTO [40, 52]. Some authors have combined additional cartilage regenerative procedures with HTO to achieve improved long-term outcomes [23, 45, 52]. However, the clinical efficacies of such procedures, including microfracture and autologous chondrocyte implantation, are debatable [5, 29, 44].

The reliability of cartilage regenerative procedures remains controversial. Several studies have questioned the advantage of augmentation for HTO and have shown that the unloading effects of HTO resulted in articular cartilage regeneration along with improved clinical outcomes [15, 22, 25]. Jung et al. demonstrated that HTO without cartilage regenerative procedures provided regeneration of fibrocartilage in the MFC articular cartilage in 147 (92%) of 159 knees at second-look arthroscopic assessment [25]. However,

Table 2 Demographic characteristics

	BMAC group (n = 55)	hUCB-MSC group (n = 55)	p value[a]
Women (no. [%])	38 (69.1)	42 (76.3)	0.391
Age (year)	55.0 ± 7.3	56.4 ± 5.3	0.310
BMI (kg/m^2)	27.2 ± 3.9	26.8 ± 3.2	0.512
Operation side: left (no. [%])	30 (54.5)	31 (56.4)	0.848
Tobacco use (no. [%])	19 (34.5)	13 (23.6)	0.207
Defect size: MFC (cm^2)	6.4 ± 3.1	6.2 ± 2.4	0.862
Meniscus status			0.889
Intact	4	3	
< 1/3 resected	28	30	
> 1/3 resected	23	22	
Surgery time (min)	77.2 ± 14.2	77.0 ± 13.2	0.917
Interval between index surgery and removal surgery (months)	17.2 ± 3.9	16.4 ± 3.4	0.409
Follow-up duration (months)	34.2 ± 8.4	31.0 ± 6.0	0.111

Values are given as means and standard deviations unless otherwise indicated

BMAC bone marrow aspirate concentrate, *hUCB-MSC* human umbilical cord blood-derived mesenchymal stromal cell, *BMI* body mass index, *K–L* Kellgren–Lawrence, *MFC* medial femoral condyle

[a]Independent t test was used to analyze differences in BMI and surgery time. Mann–Whitney U test was used to analyze differences in gender, age, defect size, interval between index surgery and second-look arthroscopic surgery at the time of plate removal, and follow-up duration. Chi-squared or Fisher´ exact test was used to analyze differences in sex, operation side, tobacco use, and meniscus status

complete regeneration of fibrocartilage was achieved in the MFC articular cartilage in 6 (4%) of 159 knees. Goshima et al., in a study investigating changes in bone tracer uptake following HTO, reported that HTO reduced bone tracer uptake of the medial compartment, which correlated with clinical outcomes [22]. Those authors suggested that the unloading effects of HTO led to pain relief, regardless of cartilage regeneration.

On the other hand, articular cartilage regeneration using MSCs has been suggested to provide good cartilage regeneration and improved outcomes [8, 20, 21, 24, 32, 34, 43, 49, 50]. Jin et al. reported that concomitant microfracture with BMAC resulted in superior cartilage compared to that produced by microfracture alone in patients undergoing HTO based on second-look arthroscopic findings. They concluded that BMAC augmentation had a synergistic effect for better cartilage regeneration. Gigante et al. demonstrated an increase in defect filling and the rate of hyaline-like cartilage regeneration after BMAC augmentation along with microfracture [19]. In a case series of 25 patients with large full-thickness articular cartilage lesions treated with BMAC and a second-generation matrix by Gobbi et al. [20], 1-step surgery restored cartilage defects and provided good functional outcomes at a minimum follow-up of 3 years. However, despite the good outcomes associated with BMAC, several studies have raised concerns regarding its ability to treat cartilage lesions due to its < 0.1% composition of stromal cells [54]. Mesenchymal cells are present in BMAC; however, they lack stromal cell differentiation activities. Hence, they do not meet the criteria for characterization of MSCs [9]. In addition, no standard technique or protocol for bone marrow aspirate harvesting exists. Commercially available systems, including centrifuges, do not provide equivalent cell numbers and concentrations. The ideal volume of the required BMAC for the treatment of a specific defect volume remains to be determined [39]. Overall, although BMAC may have some regenerative potential for cartilage, it is not enough to fully restore hyaline cartilage [9].

hUCB-MSCs can be used for articular cartilage regeneration and have some advantages over BMAC [16, 28]. Song et al. demonstrated that hUCB-MSCs combined with HTO resulted in satisfactory short-term clinical outcomes and cartilage regeneration in 25 patients aged > 60 years with medial compartment osteoarthritis [50]. Park et al. evaluated the efficacy of hUCB-MSCs for cartilage repair in seven osteoarthritic knees over a 7-year follow-up and reported improved clinical outcomes without deterioration of cartilage regeneration or significant complications [43]. In the present study, second-look arthroscopic outcomes in the hUCB-MSC group were better than those in the BMAC group. This difference may be attributed to the advantages of hUCB-MSC implantation over BMAC augmentation because of its higher proliferation rate, karyotype stability after expansion, and chondrogenic potential.

In this study, the hUCB-MSC implantation procedure provided superior articular cartilage regeneration compared to the BMAC augmentation procedure in patients who underwent HTO based on second-look arthroscopic findings, although both regenerative procedures improved cartilage regeneration compared to isolated HTO or HTO with other additional regenerative procedures in previous studies [24, 25, 29, 32, 33]. Recent studies have described a positive correlation between cartilage regeneration and clinical outcomes after HTO [32, 34, 35], which is consistent with the results of this study. Thus, hUCB-MSC application should be considered a useful additional treatment for improved cartilage regeneration that results in better HTO outcomes.

There were significant improvements in all clinical assessments in both groups, which is consistent with the outcomes reported in other case series with comparable follow-up times [8, 24, 50]. Moreover, the patients in this study achieved better clinical outcomes than those reported in previous studies [24, 32–34, 37, 41, 55]. Medial knee joint pain improved because HTO reduced the load on the medial

Table 3 Comparison of Clinical Outcomes in the BMAC and hUCB-MSC groups

	Preoperatively			Latest follow-up		
	BMAC ($n=55$)	hUCB-MSC ($n=55$)	p value[a]	BMAC ($n=55$)	hUCB-MSC ($n=55$)	p value[a]
KOOS						
Pain	42.3 ± 3.7	41.4 ± 6.5	0.408	81.7 ± 6.4	83.1 ± 8.3	0.119
Symptoms	40.9 ± 5.1	39.5 ± 6.9	0.346	79.2 ± 7.5	79.4 ± 8.8	0.748
Activities of daily living	52.0 ± 7.1	51.5 ± 8.4	0.430	82.4 ± 5.0	83.1 ± 5.8	0.393
Sports and recreation	23.8 ± 7.0	23.7 ± 9.2	0.230	62.0 ± 11.9	63.2 ± 10.7	0.256
Quality of life	31.1 ± 4.8	29.8 ± 6.3	0.152	72.4 ± 6.8	73.8 ± 8.7	0.279
SF-36						
Physical function	40.6 ± 6.3	39.5 ± 7.4	0.136	61.6 ± 7.6	63.7 ± 8.0	0.140
Role physical	42.7 ± 6.0	42.2 ± 11.8	0.639	64.7 ± 9.4	64.9 ± 13.0	0.170
Bodily pain	39.1 ± 6.1	38.5 ± 9.8	0.310	68.2 ± 8.9	68.4 ± 8.6	0.663
Social function	69.4 ± 16.6	68.1 ± 17.8	0.504	71.1 ± 16.8	71.2 ± 19.3	0.904
General health	46.2 ± 8.1	45.7 ± 10.8	0.993	64.3 ± 7.7	64.4 ± 11.2	0.385
Mental health	54.7 ± 11.4	55.0 ± 13.3	0.365	61.1 ± 13.7	62.2 ± 8.7	0.228
Role emotional	57.7 ± 15.7	58.1 ± 12.9	0.194	62.3 ± 15.5	62.6 ± 12.1	0.270
Vitality	47.0 ± 6.2	47.0 ± 11.6	0.980	61.5 ± 9.5	62.8 ± 10.3	0.131
SF-36 PCS	42.2 ± 3.5	41.5 ± 5.5	0.624	64.7 ± 5.9	65.4 ± 7.9	0.073
SF-36 MCS	57.2 ± 8.0	57.0 ± 9.2	0.978	64.0 ± 8.7	64.7 ± 8.8	0.320
IKDC	36.2 ± 3.0	35.4 ± 5.5	0.253	72.8 ± 5.8	73.3 ± 9.8	0.092
Tegner activity scale score	2.3 ± 0.9	2.2 ± 0.8	0.109	4.0 ± 0.5	4.1 ± 0.5	0.858

Values are given as means and standard deviations

BMAC bone marrow aspirate concentrate, *hUCB-MSC* human umbilical cord blood-derived mesenchymal stromal cell, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *SF-36 PCS* Short Form-36 Physical Component Summary, *SF-36 MCS* Short Form-36 Mental Component Summary, *IKDC* International Knee Documentation Committee

[a]Mann–Whitney *U* test for analysis of difference

side of the knee joint by moving the joint reaction force from the medial to the lateral side of the knee. In addition, the anti-inflammatory effects caused by cartilage regeneration via BMAC augmentation or hUCB-MSC implantation procedure and pain relief caused by paracrine effects should be considered. Despite quantitative and qualitative differences in the regenerated articular cartilage between these two treatments, there were no meaningful differences in clinical outcomes. A larger study with a longer follow-up period is needed for a more comprehensive analysis. In addition, because hUCB-MSC implantation costs approximately 5300 US dollars or more on average than BMAC, the choice of surgical treatment should be left to the patient.

Limitations

This study has several limitations. First, a relatively small number of patients participated in this clinical trial. Second, this was a retrospective cohort study based on the database of a single institute. Despite PS matching analysis, the results could have been influenced by other unmatched or uncontrolled factors, such as patient salary, occupation, daily activity level, and participation in sports and recreational activities. However, PS matching is a convincing method to minimize bias owing to the difficulties of blinded randomized trials, and the common preoperative parameters, including sex, age, BMI, and the MFC defect size, were matched in this study to increase the sample quality [4]. Third, the mean follow-up period was 33.0 months, which is not long enough to evaluate the long-term clinical outcomes and survivorship of HTO. Fourth, the absence of a control group that underwent neither the BMAC nor hUCB-MSC procedure and the nonrandomized design of the present study may have biased the interpretation of the findings. Future prospective randomized studies that include HTO alone as a third control group would be needed to clarify the real effectiveness, value, and indications of these cartilage augmentation procedures for patients with medial compartment knee osteoarthritis. Fifth, all patients received a recommendation to undergo second-look arthroscopic surgery along with plate removal to evaluate cartilage status before initial HTO; however, some patients did not agree to receive follow-up procedures. Accordingly, there was a discrepancy in the dropout rate before second-look arthroscopy between the groups, though the difference was not

Table 4 Comparison of radiologic outcomes in the BMAC and hUCB-MSC groups

	BMAC group ($n=55$)	hUCB-MSC group ($n=55$)	p value[a]
HKA angle[b]			
Preoperative	7.6 ± 2.9	7.5 ± 2.7	0.831
Latest follow-up	− 1.5 ± 2.3	− 1.6 ± 2.2	0.835
Posterior tibial slope			
Preoperative	7.7 ± 2.4	7.9 ± 2.1	0.635
Latest follow-up	8.5 ± 2.5	8.2 ± 2.5	0.471
MPTA			
Preoperative	84.7 ± 2.2	84.6 ± 2.2	0.904
Latest follow-up	92.7 ± 2.7	92.1 ± 3.4	0.265
Initial cartilage status[c] (n)			0.463
Grade 3	5	3	
Grade 4	50	52	

Values are given as means and standard deviations

BMAC bone marrow aspirate concentrate, *hUCB-MSC* human umbilical cord blood-derived mesenchymal stromal cell, *HKA* hip–knee–ankle, *MPTA* medial proximal tibial angle

[a]Independent t test was used to analyze differences in radiographic results. The Fisher´s exact test was used to analyze differences in initial cartilage status

[b]A positive angle represents varus alignment, and a negative angle represents valgus alignment

[c]Initial cartilage status was graded at the time of initial high tibial osteotomy according to the International Cartilage Repair Society grading system

statistically significant (n.s.). Additional studies with more patients are necessary. Sixth, there was also a discrepancy in the follow-up periods over which second-look arthroscopic findings (mean: 17 months) and postoperative clinical outcomes (mean: 33 months) were compared, which might have influenced the results. Despite these limitations, the strength of this study was that clinical, radiological, and arthroscopic outcomes were compared by adjusting patient baseline characteristics with PS matching. In addition, two different arthroscopic grading systems (ICRS CRA grading and Koshino staging systems) were used for comprehensive evaluation of cartilage regeneration during the second-look arthroscopic procedure. Therefore, the present study can potentially provide evidence for the efficacy of HTO with hUCB-MSC implantation in cartilage regeneration for the treatment of medial compartment osteoarthritis.

Conclusion

Clinical outcomes improved after HTO regardless of whether hUCB-MSCs or BMAC was administered. 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, compared to BMAC augmentation in patients undergoing HTO, hUCB-MSC implantation resulted in superior articular cartilage regeneration according to ICRS CRA grades, which significantly correlated with clinical outcomes. Further, the present study is significant in that it provides certain information for both orthopaedic surgeons and patients regarding the effectiveness of hUCB-MSC implantation for cartilage regeneration in medial compartment knee osteoarthritis.

Table 5 Comparison of articular cartilage regeneration on second-look arthroscopy

	BMAC group ($n=37$)	hUCB-MSC group ($n=44$)	p value[a]
ICRS CRA grading system			0.040
Grade 1: normal	1 (2.7%)	4 (9.1%)	
Grade 2: nearly normal	20 (54.1%)	30 (68.2%)	
Grade 3: abnormal	11 (29.7%)	10 (22.7%)	
Grade 4: severely abnormal	5 (13.5%)	–	
Koshino staging system			0.057
Stage A: no regeneration	4 (10.8%)	–	
Stage B: partial regeneration	12 (32.4%)	12 (27.3%)	
Stage C: total regeneration	21 (56.8%)	32 (72.7%)	

Values are presented as No. (%)

BMAC bone marrow aspirate concentrate, *hUCB-MSC* human umbilical cord blood-derived mesenchymal stromal cell, *ICRS CRA* International Cartilage Repair Society Cartilage Repair Assessment

[a]Chi-squared or Fisher´s exact test was used to analyze differences

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Compliance with ethical standards

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

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Hwasun Chonnam National University Hospital approved this study.

Informed consent Written informed consent for participation in the study was obtained from all patients, including permission to access patient's records and publish individual clinical details.

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