Autologous Bone Marrow Mesenchymal Cell Induced Chondrogenesis for the Treatment of Osteoarthritis of Knee

Sung Woo Huh¹, Asode Ananthram Shetty², Jang Mook Kim^{3*}, Mi-La Cho⁴, Seon Ae Kim¹, Siyoung Yang⁵, Young Ju Kim⁶, Palaksha Kanive Javaregowda⁷, Nam Yong Choi¹, Jin Kang¹, Seok Jung Kim^{1*}

¹Department of Orthopaedic Surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea

²Canterbury Christ Church University, Institute of Medical Sciences, Faculty of Health and Wellbeing, Kent, United Kingdom

³Department of Health Administration, College of Health Science, Dankook University, Cheonan, Korea

⁴Department of Life Science, College of Medicine, Rheumatism Research Center, Laboratory of Immune Network, The Catholic University of Korea, Seoul, Korea

⁵Department of Pharmacology, Ajou University School of Medicine, Suwon, Korea

⁶Department of Nursing Education & Administration, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, Korea

⁷Biomedical Research Coordinator, SDM College of Medical Sciences & Hospital, Sattur, Dharwad, India

Healthy and high quality of life has become the main issue with increasing human life span. Many biological treatments for osteoarthritis of the knee have been tried with limited success. We compared data from 7 patients who underwent total knee arthroplasty and 46 patients who underwent autologous bone-marrow mesenchymal cell induced chondrogenesis (MCIC) for osteoarthritis of grade IV of the Kellgren-Lawrence classification and grade IV of modified Outerbridge classification from 50 to 65 years of age. Clinical evaluation of the 2 groups showed significant improvement in the mean telephone Knee Society Scoring system (tKSS)-A (pain) and tKSS-B (function) scores throughout the postoperative follow-up period. There was no difference in the patients' satisfaction between the 2 groups. MCIC is a treatment option at least for delaying disease progression of osteoarthritis of the knee. *Tissue Eng Regen Med* 2016;13(2):200-209

Key Words: Osteoarthritis; Total knee arthroplasty; Chondrogenesis; Mesenchymal cell induced chondrogenesis; Economy

INTRODUCTION

Total knee arthroplasty (TKA) is an important option to relieve pain and restore the function of advanced osteoarthritis of the knee. The procedure has a high success rate and the device lasts well over a decade [1,2]. However, as the human life span is extended, revisional surgery rate is also increasing [3]. Despite the high success rate of TKA, complications such as infection, deep vein thrombosis, and implant related problems are critical issues. Furthermore, TKA is a very painful procedure and revisional surgery is even more painful [4-6].

Hence, many patients are reluctant to have this surgery and try to find other options that preserve the knee joint instead of replacement [7]. People want to live without medical illness, free from osteoarthritis. Delaying the development of osteoarthritis is thus important [8].

Many biologic treatments for cartilage defects reportedly have good results. One-stage cartilage regeneration procedures (CRPs) were introduced as a potential cell therapy [9,10]. Autologous bone-marrow mesenchymal cell induced chondrogenesis (MCIC) is one such CRP that is a single staged, arthroscopic surgery [11]. This technique uses microfracture, bone marrow aspiration concentrate (BMAC), hyaluronic acid (HA) and fibrin gel to treat articular cartilage defects. Recently, simple comparison of TKA and MCIC regardless of age showed significant clinical improvement [12].

However, one of the important goals of CRPs is delaying TKA and the targeted group is around 60 years of age. We evaluated

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***Corresponding author:** Seok Jung Kim, Department of Orthopedic Surgery, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 271 Cheonbo-ro, Uijeongbu 11765, Korea.

Tel: 82-31-820-3654, Fax: 82-31-847-3671, E-mail: peter@catholic.ac.kr

***Corresponding author:** Jang Mook Kim, Department of Health Administration, College of Health Science, Dankook University, 119 Dandae-ro, Dongnam-gu, Cheonan 31116, Korea.

Tel: 82-41-550-1471, Fax: 82-41-559-7934, E-mail: jangmook@gmail.com

advanced osteoarthritis patients aged between 50 to 65 years who were treated with MCIC. The data of TKA patients of the same age and same stage of osteoarthritis were used as reference.

MATERIALS AND METHODS

Patients

Data from 7 patients aged between 50 to 65 years who underwent TKA and 46 patients who underwent MCIC of the same age group for the treatment of Kellgren-Lawrence grade IV and modified Outerbridge grade IV osteoarthritis between June 2010 and June 2015, at a single center were included. Among the 46 MCIC patients, there were 13 males (28.3%), and 33 females (71.3%); and bilateral MCIC patients were 8 (17.4 %). The mean age of TKA patients was 60 years (SD=1.7) and that of MCIC was 56.8 years (SD=3.5). The average follow-up period was divided by 24 months, that is less than 24 months and less than 24 months (Table 1).

There was no additional surgery including TKA or high tibial osteotomy, during the follow up period. The study was approved by the Institutional Review Board (The Catholic University of Korea).

Evaluation of patient suitability for study participation (inclusion and exclusion criteria)

All included patients were between 50 to 65 years of age and showed grade IV of Kellgren-Lawrence classification in the ra-

diographs of weight bearing standing anteroposterior (AP), and 45 degree flexion posteroanterior (PA) and grade IV of modified Outerbridge classification arthroscopically (Fig. 1). The knee joint was required to be stable and without a severe deformity of >10 degrees of the valgus or varus, in the mechanical femorotibial angle of both lower extremities on standing AP radiographs.

All included patients had no clinical improvement in response to at least 6 months of prior conservative treatments (including medication, intraarticular injection, and physical therapy).

All operations were performed by a single surgeon.

The exclusion criteria included early osteoarthritis (Kellgren-Lawrence Grading Scale ≤ 3) and inflammatory arthritis with severe deformity, exceeding the above mentioned range, patellofemoral instability, >10 degree of flexion contracture, drug abuse history, and psychological problems.

Surgical technique

Cartilage regeneration

Harvesting of bone marrow

After suitable anesthesia, the patient's anterior superior iliac spine was marked, cleaned and draped. Bone marrow aspiration needle (SPASY™, CYP Biotech, Seoul, Korea) and syringes preloaded with 4 mL Anticoagulant Citrate Dextrose solution (Huons ACD Injection, Huons, Seongnam, Korea) were used to aspirate 38 mL of bone-marrow from the iliac crest. The aspiration site was injected with local anesthetic and covered with a sterile plaster. The bone marrow aspirate was centrifuged twice (BMC kit™, Revmed & CYP biotech, Seoul, Korea). The first cycle was for 6 minutes at 2700 g, followed by a second cycle for 5 minutes at 2400 g, to obtain bone marrow aspirate concentrate (BMAC).

Preparation of BMAC, HA and fibrin gel mixture

For application to the chondral defect, two 1 mL syringes are connected to a Y-shaped mixing catheter. One syringe contained 0.8 mL of fibrinogen (GreenPlast™, Greencross, Seoul, Korea) and 0.2 mL of HA (Highhyalplus, Huons, Seongnam, Korea). The second syringe contained 0.8 mL of bone marrow concentrate and 0.2 mL of thrombin (Greenplast™, Greencross, Seoul, Korea).

Arthroscopic procedures of arthritis

The knee was approached via antero-lateral and antero-medial arthroscopic portals and normal saline was infused under pressure (approximate to systolic blood pressure). A Wolf cannula (Karl Storz GmbH, Tuttlingen, Germany) was inserted superolaterally as an outflow cannula. The knee joint was system-

Table 1. General description (n=53)

Character	MCIC (n=46) n (%) or mean ($\pm$ SD)	TKA (n=7) n (%) or mean ($\pm$ SD)	P
Age	56.8 ($\pm$ 3.5)	60.0 ($\pm$ 1.7)	0.01*
<59	34 (73.9)	2 (28.6)	0.02†
≥ 60	12 (26.1)	5 (71.4)	
Gender			0.17†
Male	13 (28.3)	0 (0)	
Female	33 (71.3)	7 (100)	
Defect side			0.14†
Right	21 (45.7)	2 (48.1)	
Left	17 (37.0)	2 (36.5)	
Both	8 (17.4)	3 (15.4)	
Elapsed month	28.5 ($\pm$ 5.7)	20.7 ($\pm$ 4.8)	
<23	7 (15.2)	6 (85.7)	0.00**
≥ 24	39 (84.8)	1 (14.3)	0.00†
Satisfaction	1.5 ($\pm$ 0.7)	1.6 ($\pm$ 0.5)	0.60**

*Independent test, **Mann-Whitney test were performed, †Fisher exact test. TKA: total knee arthroplasty, MCIC: autologous bone marrow mesenchymal cell induced chondrogenesis

atically assessed and the arthritic lesions were identified, aided by pre-operative scans. Arthroscopic arthritis treatment procedures included removal of osteophyte, meniscectomy of torn and deformed menisci if observed, synovectomy, and careful debridement using curettes and shavers for arthritic chondral surface; burrs were used for the removal of the subchondral sclerotic surface. Drilling and microfracture were performed by (Arthrex Inc., Florida, CA, USA) to a depth of 3 mm, at intervals of 3 mm (Fig. 2A and B).

Application of BMAC, HA and fibrin gel mixture

Saline was drained from the knee joint and carbon dioxide (CO₂) was introduced at 20 mm Hg, at a rate of 20 L/min using the Wolf cannula (Karl Storz GmbH) and disposable tubing with a filter (Insufflation tubing with Wolf adaptor, Leonhard Lang UK Ltd., Stroud, UK) through the supero-lateral portal. Residual saline was aspirated from the knee by a 20 mL syringe and an angled suction tube under low pressure to avoid bleeding. The microfractured lesion(s) was dried with cotton buds. A 18 gauge spinal needle (inner diameter 1.2 mm, length 90 mm)

(Becton Dickinson, Madrid, Spain) was inserted into the joint via any suitable portal and was connected to the double syringe. Under arthroscopic guidance, the BMAC, HA and fibrin gel mixture was gently applied, via the double syringe, uniformly over the lesion. For patello-femoral joint lesions, a patellar clamp (Lewin bone clamp) was used to lift and stabilize the patella. Due to the tamponade effect of the CO₂ and the adhesiveness of the gel, the graft adheres to the lesion, even against gravity. If necessary, a second layer was injected deep into the firm first layer (Fig. 2C). The graft could be shaped *in situ* using a McDonalds dissector (Bolton Surgical, Sheffield, UK). The graft became firm after 5 minutes and under arthroscopic vision, the knee was then moved through its range of motion several times to anatomically sculpt the graft and test its stability (Fig. 2D). If satisfactory, the CO₂ was switched off and all instruments were withdrawn. The portal sites were injected with local anesthetic (0.5% Chirocaine) and closed with sutures. The knee was covered with a compression bandage.

Figure 1. (A) Pre-operative medial femoral condyle lesion, (B) tibial lesion, (C) osteophyte formation in intercondylar notch, and (D) trochlear lesion of in 60 year old female showed advanced osteoarthritis.

Experimental evidence for potential use of BMAC

1) Isolation of bone marrow mononuclear cells

Bone marrow aspirates were diluted 1:1 with PBS (Gibco Invitrogen, Grand Island, NY, USA) and carefully loaded onto Histopaque (1.077g/mL) (Sigma Chemical Co., St. Louis, MO, USA) to isolate bone marrow mononuclear cells (MNCs). MNCs were isolated by density gradient centrifugation (400 g, 25 min, room temperature) and washed three times with a-MEM (Gibco Invitrogen, Grand Island, NY, USA). The final resuspension was done after filtration through a 70 μ m cell strainer (Becton Dickinson/Falcon, Heidelberg, Germany).

2) Automatic cell count

The number of nucleated cells, lymphocytes, monocytes, red blood cells, platelet and neutrophil granulocytes were counted before MNC of bone marrow aspirate and BMAC isolation using a cell counter (XE2100, Cysmax, Japan). The number of MNC was calculated by summing the lymphocytes and mono-

cytes (Supplementary Table 1 in the online-only Data Supplement).

3) CFU-F assay

A colony forming units-fibroblast assay was performed to quantify non-hematopoietic fibroblastic colonies. Isolated mononucleated cells were cultured in 10 mm diameter cell culture dishes (Becton Dickinson/Falcon, Heidelberg, Germany) for 14 days at 37°C in humidified atmosphere and 5% CO₂. The medium using a-MEM (Gibco, Life Technologies, Karlsruhe, Germany) with 20% FBS (Gibco, Life Technologies, Karlsruhe, Germany), penicillin (100 U/mL; Gibco, Life Technologies, Karlsruhe, Germany) and streptomycin (100 μ g/mL; Gibco, Life Technologies, Karlsruhe, Germany).

After 14 days, adherent cells were fixed with paraformaldehyde (Biosesang, Seongnam, Korea) for 5 min washed, and stained with 1% crystal violet. Colonies were counted macroscopically and visual inspection with the plate on a white piece of paper (Supplementary Fig. 1 in the online-only Data Supplement).

Figure 2. (A) Microfractured and drilled MFC and tibial lesions. (B) Removal of osteophyte as a surgical procedure. (C) Injected BMAC mixture to MFC. (D) Injected BMAC (white arrow) to trochlear lesion. MFC: medial femoral condyle, BMAC: bone marrow aspiration concentrate.

4) Flow cytometry

Immunophenotyping of BM and BMAC was performed by flow cytometry using a FACS Calibur cytometer (BD Biosciences, Heidelberg, Germany). PE-labeled antibody (Ab): CD44, CD13, CE29, CD19, CD11 APC-labeled Ab: CD90, CD105, FITC-labeled Ab: CD34 (Supplementary Fig. 2 in the online-only Data Supplement).

Total knee joint replacement arthroplasty

TKA was performed through the midline skin incision and medial parapatellar approach. The implants were of the posterior stabilized type (Lospa, Corentech, Seoul, Korea) and femoral and tibial components were fixated by cement. Patella was not replaced.

Rehabilitation

Continuous passive motion (CPM) machines were used for rehabilitation from the day 1 post-surgery, in both groups.

Quadriceps muscle strengthening exercise was continued during the pre and post operation period. For TKA patients, partial weight bearing walking exercise with crutch or walker was started from the 2nd day post-surgery, and followed by full weight bearing, according to the patient comfort. For MCIC patients, partial weight bearing walking exercise with a crutch or walker was started from the 2nd day post-surgery, and followed by full weight bearing, beginning 6–8 weeks post-operatively. The weight bearing was protective of the operation site, and excessive weight to the lesion was prevented, to assist in cartilage regeneration. CPM was used for 30 minutes on the 1st day and daily increments of 10 minutes up to a total of 4 hours per day.

Patient evaluations

Details concerning the patients' clinical outcomes were collected using the telephone score format initially used to estimate the KSS (Supplementary Fig. 3 in the online-only Data Supplement) [13]. The above information was obtained pre-operative-

Table 2. Overall pain and function scores (n=53)

Group	Pre-pain	Post-pain	p^*	Pre-function	Post-function	p^*
	Mean ($\pm$ SD)			Mean ($\pm$ SD)		
MCIC (n=46)	24.5 (14.8)	92.2 (13.2)	0.00	34.2 (26.2)	87.0 (18.8)	0.00
TKA (n=7)	20.0 (6.7)	88.6 (10.7)	0.02	41.4 (19.5)	85.7 (19.0)	0.02

*Wilcoxon signed rank test was performed. MCIC : mesenchymal cell induced chondrogenesis, TKA: total knee arthroplasty

Table 3. The pre-post difference in pain & function in each treatment group (n=53)

Type of treatment	Pre-post pain difference	p^*	Pre-post function difference	p^*
	Mean ($\pm$ SD)		Mean ($\pm$ SD)	
MCIC (n=46)	67.7 (20.8)	0.55	52.7 (30.3)	0.49
TKA (n=7)	68.6 (10.3)		44.3 (29.9)	

*Mann-Whitney test was performed. MCIC : mesenchymal cell induced chondrogenesis, TKA: total knee arthroplasty

Table 4. Effect of variables on pre-post difference and satisfaction (n=53)

Variables	Pre-post pain difference			Pre-post function difference			Satisfaction		
	β	SE	p^*	β	SE	p^*	β	SE	p^*
Age	-0.32	0.79	0.03	-0.13	1.32	0.32	0.15	0.03	0.36
Gender									
Male	-0.22	6.00	0.10	-0.09	10.05	0.52	0.07	0.24	0.62
Female (reference)									
Defect side									
Right	0.16	5.56	0.23	0.08	11.96	0.69	-0.13	0.28	0.53
Left	0.17	5.63	0.19	-0.13	11.92	0.50	-0.01	0.28	0.97
Both (reference)									
Treatment									
MCIC	-0.21	6.68	0.19	0.07	13.32	0.66	0.02	0.31	0.90
TKA (reference)									

*Enter method multiple regression analysis was performed. MCIC : mesenchymal cell induced chondrogenesis, TKA: total knee arthroplasty

ly and during the telephone follow-up post-operatively.

Our clinicians rated the patient knee status using the standardized 100-point rating scale of the telephone Knee Society Scoring system (tKSS) regarding pain (A) and function (B). Data on adverse events regardless of relatedness to surgery were collected and included in the analysis.

Statistical analysis

Categorical variables were presented as numbers and percentages, and continuous variables were expressed as mean $\pm$ SD and range. Categorical variables were analyzed using the Fisher exact test. The nonparametric Wilcoxon signed rank test was used for the comparison of means between the 2 groups based on the result of test for normality. The Mann-Whitney U test was used for the general mean comparison between the 2 groups. For parametric test, the mean comparison between 2 groups was by independent t-test. Categorical variables after Dummy parameterization were analyzed using the Enter method multiple regression analysis, two-way ANOVA to determine the pattern and relative influence among the variables. SPSS software version 14.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses.

RESULTS

Patients

The number of MCIC patients was 46 with the mean age of 56.8 years (SD=3.5). The number of TKA patients was 7 with the mean age of 60 years (SD=1.7). The age difference in the two groups showed a statistical significance, where TKA patients were older than MCIC patients ($p=0.01$).

The age variable was divided into 2 groups: there were more patients less than 60 years old in MCIC and more patients older than 60 years old in TKA.

The difference in the follow-up period between the two group showed a statistical significance ($p<0.01$) and the average follow-up period was divided by 24 months. MCIC had a longer follow-up period of average 28 months, while the 84.8% patients had the follow-up period over 24 months.

Females were predominant and there was no statistically significant difference between the 2 groups in the patients' satisfaction, sex, lesion side (Table 1).

Clinical outcome

Clinical evaluations in the 2 groups showed significant improvement in the mean tKSS-A (pain) and tKSS-B (function) scores for all post-operative data throughout the follow-up period (Table 2).

There was no statistically significant difference in the degree of improvement between the 2 groups (Table 3). In the analysis of the relative influence of patient characteristics and treatments on the improvement of pain, function, and satisfaction, only age variable showed a contrary relationship ($p=0.03$). The young age showed better pain improvement and other variables such as sex, side of lesion, and treatment method showed no effect on the pain, function, and satisfaction (Table 4).

The age variable was divided into 2 groups. The improvement of pain showed a statistically significant difference in age groups ($p=0.03$). Patients younger than 60 years of age showed a better improvement in pain relief compared to those older than 60 years of age, with no statistically significant difference between the 2 treatment methods (Table 5).

The pain and functional improvements of each treatment method according to the follow-up period were not significantly different, but TKA showed a tendency of improved pain when compared to MCIC, according to the follow-up period.

MCIC showed a tendency of improved function when compared to TKA, but TKA showed a marked improvement in function after 2 years of follow-up period (Table 6 and 7).

Adverse events

There was no adverse event.

DISCUSSION

TKA has been the mainstream treatment for osteoarthritis of the knee for the past several decades and will be the gold standard of treatment for severe and deformed arthritis in the fu-

Table 5. Pain differences between treatments according to age (n=53)

Source	SS	df	MS	F	p^*
Treatment	411.65	1	411.65	1.31	0.26
Age grade	1613.15	1	1613.15	5.15	0.03
Treatment $\times$ age grade	87.10	1	87.10	0.28	0.60
Error	15350.33	49	313.27		
Total	264030.00	53			

*Two-way ANOVA, Scheffe post hoc test was performed

ture. It is one of the most successful surgical procedures, and more than 90% of patients have pain relief, and improved knee motion and function [14]. Long-term follow up of TKA provides relief to the patients and helps to expand the indication of TKA to the younger patients [15].

Despite these successful results, complications after TKA are very critical issues [16-18]. Infection, deep vein thrombosis, pulmonary embolism, surgical-procedure related problems such as malalignment and gap imbalance are debilitating. These complications require specific treatments ranging from medication to re-operation. The pain after surgery is very severe and has been addressed by several research studies [19,20]. Many successful results of TKA are reported. However, since the concerns and priorities of patients differ from those of surgeons it is difficult to evaluate the success of TKA due to subjective nature of satisfaction [21]. Since many patients suffer from continuous pain after TKA, and the revisional surgery findings often reveal abnormal tissue formation, osteolysis, various inflammations, we accordingly try to find an alternative treatment for osteoarthritis [7]. Even though TKA longevity is extended, the chance of revisional TKA has increased with increased life span. There are high risk complications related to the revisional TKA, and operations are very painful [22]. Many patients are reluctant to receive TKA due to these complications, and thus, both patients and surgeons prefer alternative treatments that can preserve the knee joint instead of replacement.

Therefore, biological treatments such as stem cell treatments, cultured cell therapy, and bone marrow cell concentrations have become popular currently. Cultured cell therapies like autologous chondrocyte implantation (ACI) or matrix induced ACI

are good treatment options for articular cartilage defects [23]. However, they require 2 surgeries, i.e., tissue harvest operation followed by cell culture and implantation operation. The recovery is often prolonged and expensive due to the cell culture process and 2 operations. Also, there are few reports regarding the treatment of arthritis using ACI [24].

Ease and effectiveness by single-stage minimal invasive treatments are necessary for patient satisfaction. Cartilage regeneration operations based on the arthroscopic marrow stimulation procedure such as microfracture or multiple drilling were introduced and short-term results were reported.

Microfracture is a technique that covers injured articular cartilage through the proliferation and differentiation of bone marrow derived mesenchymal cells [25]. Microfracture is simple, minimally invasive using arthroscopy, and a cost effective first-line treatment option for focal cartilage defects [26]. The theoretical basis of this procedure is that the hematoma from the penetrated bone marrow contains marrow stromal cells including mesenchymal stem cells that differentiate into chondrocytes and synthesize cartilage.

This study extended this single stage minimally invasive surgery for focal cartilage defect to osteoarthritis treatment. A mixture of concentrated bone marrow cells, HA and fibrin were used for cartilage regeneration after arthroscopic microfracture.

Firstly, routine arthroscopic surgery including the removal of osteophyte, synovectomy, debridement, microdrilling and microfracture of arthritic surface of cartilage, was conducted (Fig. 2A and B). Under continuous CO₂ inflation, a mixture of concentrated bone marrow cells, HA and fibrin without another skin incision was injected through arthroscopic portals to the

Table 6. Pain differences between treatments according to elapsed month (n=53)

Source	SS	df	MS	F	<i>p</i> *
Treatment	85.36	1	85.36	0.21	0.65
Elapsed year	121.81	1	121.81	0.30	0.59
Treatment×elapsed year	3.78	1	3.78	0.01	0.92
Error	19828.62	49	404.67		
Total	264030.00	53			

*Two-way ANOVA was performed

Table 7. Function differences between treatments according to elapsed month (n=53)

Source	SS	df	MS	F	<i>p</i> *
Treatment	0.13	1	0.13	0.10	0.76
Elapsed year	0.39	1	0.39	0.05	0.82
Treatment×elapsed year	0.28	1	0.28	0.02	0.89
Error	24.79	49	0.51		
Total	149.00	53			

*Two-way ANOVA was performed

prepared arthritic surface (Fig. 2C).

Continuous CO₂ inflation is the key to this technique. Clinically, CO₂ gas is safely used in laparoscopic surgery, where intraarticular positive pressure of CO₂ gas facilitates the attach-

ment of the injected mixture to the articular surface. After the attachment of the mixture to the surface, the fibrin in the mixture leads to consolidation via the action of fibrinogen and thrombin, and then BMAC can be attached in the defect area

Figure 3. (A) Pre-operatively, both knee standing anteroposterior (AP) radiographs of 60 year-old lady show medial joint space obliteration with osteophyte formation indicating advanced osteoarthritis of right knee. (B) Both knee standing AP radiographs obtained 12 months after MCIC of right knee show widening of medial joint space and improvement of varus deformity. MCIC: mesenchymal cell induced chondrogenesis.

Figure 4. (A and B) Pre-operatively, MRI scan of right knee showed degenerative tear of medial meniscus, large amount of joint effusion, grade 4 cartilage defect of medial femoral condyle, medial tibia condyle and patella facet, and multiple osteophyte formation indicating tricompartmental osteoarthritis. (C and D) Right knee MRI scan obtained 34 months after MCIC of right knee showed markedly improved joint effusion and cartilage like tissue formation restoring articular cartilage thickness of medial femoral condyle, medial tibial condyle, and trochlear. MCIC: mesenchymal cell induced chondrogenesis.

without additional procedure (Fig. 2D).

A new articular surface could be formed through controlling the speed, direction, and location of injection. With this technique, all knee cartilages including the cartilage of patella and posterior femoral condyle are accessed without a skin incision.

Microfracture is a simple, easy and effective procedure for small lesions of articular cartilage. For large lesions, newly formed cartilage after microfracture is scanty and brittle. The injected concentrated bone marrow cells could participate in articular cartilage regeneration to overcome this limitation of microfracture alone. Also, HA of a mixture improves repair potential, leading to a more hyaline-like repair tissue, with better defect fill and adjacent area integration (Fig. 4) [27]. The newly introduced operation technique using continuous CO₂ inflation and the injection of the mixture into the cartilage lesion leads to rapid recovery.

In this study, the patients who received MCIC could be TKA candidates because they had advanced osteoarthritis of knee. However, they chose the CRP instead of TKA after receiving an explanation of the surgical procedure. Despite possibilities of the failure of MCIC for the treatment of osteoarthritis, as compared to focal cartilage defect, patients preferred avoiding TKA and delayed replacement operation.

Patients were carefully selected to increase the possibility of procedural success. The candidates did not have severe valgus or varus deformity that needed corrective osteotomy (Fig. 3), had enough spare time for rehabilitation, and were willing to follow surgeon's instructions. The previously defined optimal age for TKA was older than 60 years [28]. However, if the increased life span is considered, the optimal age of TKA should be older than 70 years. Therefore, the age groups who can have benefits of evading or delaying TKA range between 50 to 60 years old. In this study, the evaluated age group of 50 to 65 years old showed results comparable to TKA. If TKA is delayed or avoided, the socioeconomical benefits are significant [29].

The weak point of this study was the small number of patients that made it difficult to conclude that MCIC was a good treatment option for osteoarthritis. However, MCIC was possibly an effective replacement of TKA for the treatment of osteoarthritis without severe deformity. This study will facilitate further development of CRPs to substitute total joint replacement operation.

Supplementary Materials

The online-only Data Supplement is available with this article at <http://dx.doi.org/10.1007/s13770-016-9125-y>.

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Conflicts of Interest

The authors have no financial conflicts of interest.

Ethical Statement

The study was approved by the Institutional Review Board at The Catholic University of Korea (Permit Number: UC13Q-IS0154).

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