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ORIGINAL ARTICLE

Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee

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Abstract
Purpose As a treatment method of degenerative arthritis of knee, this study evaluated the clinical efficacy of the intra-articular injection of autologous bone marrow aspirates concentrate (BMAC) with adipose tissue.
Materials and methods Between April 2011 and May 2012, 41 patients (75 knees) who were diagnosed as a degenerative knee arthritis and underwent the BMAC injection with adipose tissue were included in this study. Mean age was 60.7 years old (ranged 53–80). Kellgren–Lawrence grade was used for assessing radiologic degree of osteoarthritis; there were each 12, 24, 33, and 6 cases of grade I, II, III, and IV. At preoperative and postoperative 3, 6, and 12 months, pain score using visual analogue scale (VAS) and functional scales were used for evaluation.
Results After the procedure, mean VAS score was decreased from 7.0 preoperatively to 4.1, 3.5, and 3.3 postoperatively 3, 6, and 12 months. And functional scores were also improved; International Knee Documentation Committee score (from 37.7 preoperatively to 59.3, 66.3, 69.3 postoperatively), SF-36 health score (from 31.5 to 43.5, 45.6, 47.7), knee and osteoarthritis outcome score (from 43.1 to 64.9, 68.5, 70.6), Lysholm Knee Questionnaire (from 37.3 to 65.4, 68.6, 71.0) were all increased after the procedure. When classified according to K–L grade, the improvement of VAS score in grade IV group was 8.2 preoperatively to 5.5, 5.3, and 5.7 postoperatively, which was significantly poorer than those of grade I–III groups. In the knee functional scales, similar pattern was checked.
Conclusions BMAC injection significantly improved both knee pain and functions in the patients with degenerative arthritis of knee. Also, the injection would be more effective in early to moderate phases.

Keywords Knee · Arthritis · Bone marrow aspirates concentrate (BMAC) · Intra-articular injection

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Introduction

Degenerative arthritis of knee is one of the most common musculoskeletal disorders in adults, and treatment modalities for injured articular cartilage are variable [1–4]. Current treatment for early phase of degenerative arthritis focuses on relief of symptoms, rather than improvement of biochemical environment of joints, and its modalities are usually conservative treatments using medication such as NSAIDs, glucosamine, hyaluronic acid, and steroids [5, 6]. Conservative treatment methods have been much improved, but ultimately could not prevent progression of the disease. With recent increase of interest in field of regenerative medicine, many studies about regeneration of articular cartilage using stem cells are actively underway. Initial method was mainly culture, for differentiation and proliferation of mesenchymal stem cells, but its disadvantage such as complexity and high cost of the procedure were also existed [7, 8]. Recently, therefore, extraction of the mesenchymal stem cells obtained from autologous bone marrow followed by concentration, not culture, was introduced as a new method. And furthermore, intra-articular injection of this concentrated autologous bone marrow aspirates with use of autologous adipose tissue as scaffold into the knee joint is rarely reported world widely about its clinical results.

In this article, therefore, we report therapeutic outcomes of autologous bone marrow aspirates concentrate (BMAC) injection as the treatment for degenerative arthritis of the knee.

Materials and methods

From April 2011 to May 2012, in Kosin University Gospel Hospital, outpatients with chief complaint of knee pain were performed thorough clinical history, physical and neurologic examination, laboratory test, X-ray, and MRI of the knee. Diseases of the knees included in this study were limited to osteoarthritis, and the study was performed only if the patients understood and agreed about treatment method and procedure. After careful review of all the test results, we set exclusion criteria in this study: knee instability, severe malalignment, flexion contracture of more than 10°, inflammatory arthritis such as rheumatoid arthritis and ankylosing spondylitis, presenting muscle pain, and underlying diseases such as hematologic disorders, septicemia, coagulopathy, neoplasm, active infection, and immune deficiency.

According to these criteria, 41 patients (75 knees) who were diagnosed as degenerative arthritis of the knee in our hospital and were followed up at least 6 months after BMAC injection by corresponding author were included in this study. Mean age was 60.7 years, ranging from 53 to 80 years, and there were 17 (41.5 %) males and 24 (58.5 %) females. Mean follow-up period was 8.7 months, ranging from 6 to 19 months. Degree of the degenerative arthritis was evaluated by K–L grade (Kellgren–Lawrence grading scale) on standing anteroposterior (AP) view: there were 12 (16.0 %) cases of grade I, 24 (32.0 %) cases of grade II, 33 (44.0 %) cases of grade III, and 6 (8.0 %) cases of grade IV. In the procedure and surgical methods, BMAC with adipose tissue injection alone was performed in 63 (84.0 %) cases, which were most. In addition, the injection with arthroscopic debridement was performed in 6 (8.0 %) cases, with arthroscopic microfracture in 5 (6.7 %) cases, and with high tibial osteotomy in 1 (1.3 %) case.

For the procedure, the patient was placed with supine position, following preparing and draping of anterior superior iliac spine (ASIS) or posterior superior iliac spine (PSIS) of pelvis, then local anesthesia from skin to periosteum. Autologous bone marrow of 120 cc is aspirated from ASIS or PSIS of the pelvis by using SmartPReP2 Bone Marrow Procedure Pack BMAC2 kits (Harvest Technology, USA). The punctured bone marrow was injected into the plastic bag including the anti-coagulant inside the kit and then was mixed. The SmartPReP2 Platelet Concentration System (Harvest Technology, USA) was used to suppress the increase in temperature of bone marrow and to separate 14 cc of platelet including the autologous stem cells and growth factors. After local anesthesia in the abdomen, 20 cc of the adipose tissues were aspirated, and 7 cc of the autologous bone marrow derived mesenchymal stem cells and 10 cc of adipose tissues were injected into the each knee joint. When the arthroscopic microfracture and debridement were executed, the debridement was conducted on the borders of damaged cartilage including the healthy cartilage tissues, and the subchondral bone of lesion was exposed. Then the microfracture was conducted. After execution of the microfracture, the tourniquet was removed, and it was checked that the bone marrow containing the blood and stem cells permeated the part of operation.

After the operation, the patients were let take 3 h with bed rest and then go back home to return to their daily lives. When it is needed to control the pain, the use of oral non-steroidal anti-inflammatory drug was not allowed, and the acetaminophen pain relievers or the opioid were prescribed. There was no limitation on daily lives other than the instruction to refrain from extreme exercise for 6 weeks after the operation. However, in case of execution of microfracture, the continuous passive motion (CPM) was applied to the knee joints in the state of non-weight bearing for 6 weeks, and then the exercise was started at 30° through 60°. And then the patients themselves conducted the joint angle exercise until the full ROM (range of motion) was reached with increase by 10° through 20° per week. After that, the patients were let return to their daily lives in the state of full-weight bearing since 3 months after the operation.

The clinical evaluation was based on the survey completed at outpatient visits before the operation and 3, 6, and 12 months after the operation, the physical examination, and the survey by phone. This study evaluated the degree of pain of patients through the visual analogue scale (VAS) scores, and the clinical results were analyzed by using the International Knee Documentation Committee (IKDC)

Table 1 Pain and functional results, preoperative and postoperative 3, 6, and 12 months

Pain/functional scores	Preoperative	Postoperative 3 months	Postoperative 6 months	Postoperative 12 months
VAS score	7.0 (±0.5)	4.1 (±0.7)	3.5 (±0.6)	3.3 (±0.6)
IKDC score	37.7 (±4.4)	59.3 (±6.0)	66.3 (±5.4)	69.3 (±5.5)
SF-36 health score	31.5 (±1.7)	43.5 (±2.2)	45.6 (±2.6)	47.7 (±2.9)
KOOS score	43.1 (±6.3)	64.9 (±5.6)	68.5 (±5.1)	70.6 (±5.1)
Lysholm Knee Questionnaire	37.3 (±5.3)	65.4 (±6.0)	68.6 (±5.9)	71.0 (±6.0)

score, SF-36 (short-form 36 health survey) score, knee and osteoarthritis outcome score (KOOS), and Lysholm Knee Questionnaire/Tengner Activity scale as the knee functional scales. Cochrane–Mantel–Haenszel (CMH) test was performed to test association between ordinal-scaled categorical variables. Nonparametric analysis was performed with Wilcoxon rank sum test to analyze difference in the clinical outcomes at preoperative and 3-, 6- and 12-month follow-up between subgroups. Data were described as mean ± standard error of the mean (SEM). P values less than 0.05 were considered statistically significant, and all statistical analyses were carried out using SPSS software (SPSS 17.0, SPSS, Chicago, IL, USA) [9].

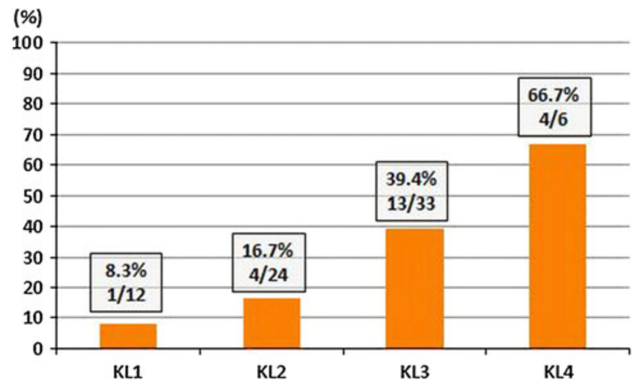

Fig. 1 Proportions of poor results according to K–L grade. It was found that participants with higher K–L grade were associated with exhibiting poorer results (CMH test p value = 0.002)

Results

As a clinical result of the total of 41 patients and 75 knees, the VAS score was decreased from 7.0 preoperatively to 4.1, 3.5, and 3.3 postoperatively 3, 6, and 12 months on the follow-up. Also, the knee functional scales were improved (Table 1). The IKDC score was increased from 37.7 preoperatively to 59.3, 66.3, and 69.3 postoperatively 3, 6, and 12 months on the follow-up, and the SF-36 Health score was increased from 31.5 preoperatively to 43.5, 45.6, and 47.7 postoperatively. The KOOS score was increased from 43.1 preoperatively to 64.9, 68.5, and 70.6 postoperatively, and the Lysholm Knee Questionnaire was increased from 37.3 preoperatively to 65.4, 68.6, and 71.0 postoperatively. All of them showed an improving aspect.

In addition, on the basis of the fact that the presence or absence and the degree of pain at the follow-up observation of patients had the closest relationship with satisfaction of the patients, this study defined the cases where the pain of patients were relieved by 50 % or more at the final follow-up compared with before the operation as the satisfactory results, and the cases where the pain before the operation still remains by 50 % or more as the inferior results. As a result of analysis following this standard, of the total 75 knees, 53 knees (70.7 %) showed a satisfactory result and 22 knees (29.3 %) showed an inferior result.

In case of classification following the K–L grade, the inferior results were shown in one knee (8.3 %) of the 12 knees of the grade I group, 4 knees (16.7 %) of the 24 knees of the grade II group, 13 knees (39.4 %) of the 33 knees of the grade III group, and 4 knees (66.7 %) of the 6 knees of the grade IV group. The patients with more advanced K–L grade showed poorer results after the procedure, which was statistically significant ($p = 0.002$) (Fig. 1).

In particular, it was found that the effect of BMAC was significantly poor in the group of K–L grade IV. While the average VAS score was decreased from 7.0 preoperatively to 4.1, 3.5, and 3.3 postoperatively 3, 6, and 12 months constantly showing more improving aspect in the groups of grade I through III, the score was decreased from 8.2 preoperatively to 5.5, 5.3 postoperatively 3, 6 months, but a little increased to 5.7 postoperatively 12 months, showing poorer relief of pain in the group of grade IV. The knee functional scales also showed a similar aspect. While the IKDC score was increased from 37.7 preoperatively to 59.3, 66.3, and 69.3 postoperatively in the groups of K–L grade I through III, the score was increased from 35.5 preoperatively to 45.1, 53.0, and 52.4 postoperatively in the group of grade IV. The SF-36 score was increased from 31.5 preoperatively to 43.5, 45.6, and 47.7 postoperatively in the groups of K–L grade I through III, but the score was increased from 25.1 preoperatively to 29.9, 31.4, and 34.9 postoperatively in the group of grade IV. The KOOS score was increased from 43.1 preoperatively to 64.9, 68.5, and

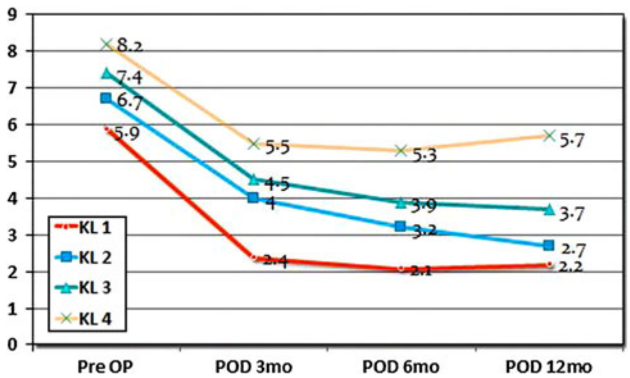

Fig. 2 VAS score according to K–L grade

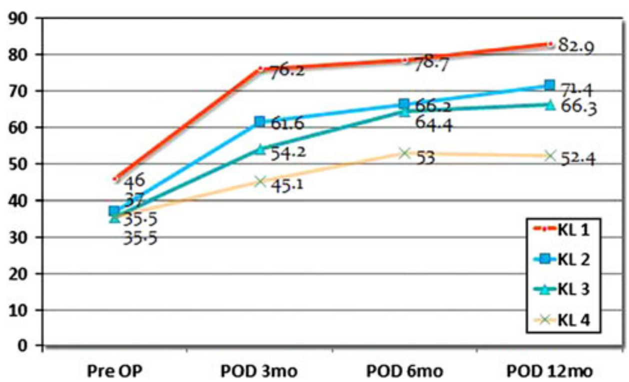

Fig. 3 IKDC score according to K–L grade

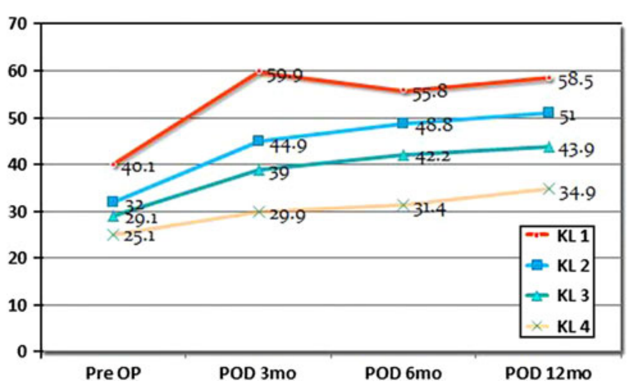

Fig. 4 SF-36 Health score according to K–L grade

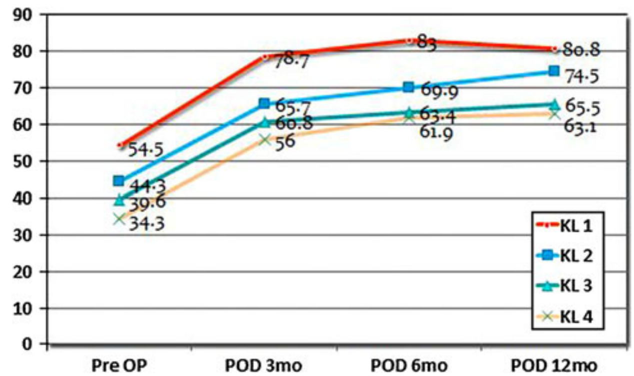

Fig. 5 KOOS score according to K–L grade

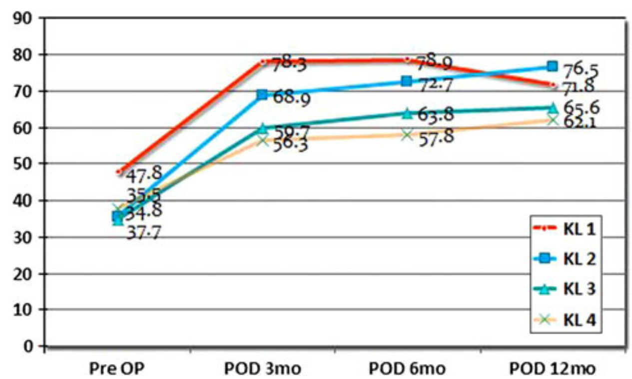

Fig. 6 Lysholm Knee Questionnaire according to K–L grade

70.6 postoperatively in the groups of K–L grade I through III, but the score was increased from 34.3 preoperatively to 56.0, 61.9, and 63.1 postoperatively in the groups of grade IV. Also, while Lysholm Knee score was increased from 37.3 preoperatively to 65.4, 68.6, and 71.0 postoperatively in the groups of K–L grade I through III, the score was increased from 37.7 preoperatively to 56.3, 57.8, and 62.1 postoperatively, showing a relatively inferior result in the groups of grade IV. The result of analysis by dividing into the four groups of K–L grade I, II, III, and IV was also similar to that, and when the K–L grade was lower, that is, when the degenerative arthritis was in the earlier stage, the VAS score was lower and the knee functional scales were higher (Figs. 2, 3, 4, 5, 6).

However, when classifying by age, the groups of patients that showed a satisfactory result were 61.0 years old on average, and the groups of patients that showed an inferior result were 62.7 years old on average. Thus, when the patients were older, the results were somewhat inferior, but they showed no statistical significance.

It was found that the common side effects occurring after the procedure were joint swelling (69 knees, 92.0 %) and pain (31 knees, 41.3 %). The swelling appeared as the symptom of the reactive synovitis inside the knee joints that occurred after the injection of BMAC and adipose tissues and occurred 2 weeks on average (1.5 through 4 weeks) after the procedure. It lasted for about 8 weeks (2 through 13 weeks) and then improved. When the symptom occurred, we did not perform the arthrocentesis nor the steroid injection, but conducted the injection of platelet-rich plasma (PRP) or hyaluronic acid. In addition, the patients complained of pain in 31 knees, which occurred 1.3 weeks on average (immediately after the procedure through 4 weeks) after the procedure and lasted for about

4 weeks (2 through 9 weeks). In this case, this study prohibited the use of non-steroidal anti-inflammatory drug, instead administered the opioid or acetaminophen pain reliever and anti-inflammatory drugs orally and performed the PRP injection. This use of PRP came from the anti-inflammatory and pain relieving effects of PRP [10].

Of the 22 knees (29.3 %) that showed a clinically inferior result also 6 months after the procedure, there were 6 patients with remaining varus deformity of knee joints, 2 patients with the history that received an operation and chemotherapy because of synovial sarcoma at wrist and rectal cancer, and one patient who was tested positive for rheumatoid factor. For 4 patients of the patients who showed an inferior result, the additional operations such as total knee arthroplasty, high tibial osteotomy, and unicondylar knee arthroplasty were finally performed.

Discussion

The articular cartilage has no blood vessel, nerve, nor lymphatic vessel, and has almost no cartilage-derived cell since the adulthood. Thus, it is known to have remarkably poorer regenerative ability than other tissues, and its treatment process is different from one of other tissues and is a subject of many studies and controversies [11–13]. The treatment so far has been focusing on the improvement of symptoms rather than on the improvement of biochemical environment of joints in reality. As the treatment methods for damaged cartilage, the non-operative treatments including the NSAIDs, glucosamine, hyaluronic acid, and steroid are known to be effective. The operative treatments include the bone marrow stimulation and the whole tissue transplantation technique. Of these, since the late 1990s, the microfracture using the arthroscope has been used for the regeneration of damaged articular cartilage. The principle is to make a hole passing through the subchondral plate, to put the bone-marrow-derived mesenchymal stem cell into the parts surrounding the cartilage, to induce the regeneration of cartilage, and to thereby reduce the local pressure inside the cartilage to reduce the damages [14]. This has an easy procedure, and its clinical superiority and the histological regeneration of cartilage are identified. However, there is a limitation on the size of part with defect of cartilage at the time of operation, and the effects are known to be decreased in the sizes over 6 cm^2. It is also reported to have a bad result in the patients 50 years old or older because the concentration of mesenchymal stem cells gets decreased with age [15–17]. Finally, there is also a weak point that the regenerated fibrocartilage is made of the fibrocartilage and hyaline-like cartilage with a low content of type II collagen, which are different from the normal hyaline cartilage [18].

In order to overcome these weak points, the treatment to regenerate the damaged cartilage using the adult stem cells collected from the autologous bone marrow was developed. Stem cells are divided into the adult stem cells, which are in various tissues of our body since when we are born, and the embryonic stem cells that are started in the fertilized egg in which the sperm and the egg are combined [19]. The places where the mesenchymal stem cells exist inside the human body include bone marrow, fat, peripheral blood, and synovial membrane. The mesenchymal stem cells have the ability to regenerate and restore the damage tissues. In particular, the mesenchymal stem cells are known to differentiate into the chondroblast in the cartilage tissues, into the fibroblast in the skin and the connective tissues (tendon, ligament), and into osteoblast in bones, and then to regenerate. In 40 cc of bone marrow, 1.2 × 109 mononuclear cells and 2.4 × 104 mesenchymal stem cells exist, and in 1 cc, 600 mesenchymal stem cells exist. In 200 cc of adipose tissues, 4 × 108 mononuclear cells exist, and in 1 cc, 500 mesenchymal stem cells exist, which are 5 through 10 times of those in the bone marrow [20].

According to the animal study of Agung, the ideal number of mesenchymal stem cells that are needed for the regeneration of cartilage is known to be 1×10^7, and a few clinical studies report that 1×10^7 or more adult stem cells are ideal [8, 21–24]. However, though the method to culture the adult stem cells can obtain a sufficient number of them, it can lose the ability of differentiation or there can be the possibility of transformation into a malignant one. Also, the process is complicated, and a great cost is spent [7, 8]. The allogenic stem cells have complex harvest and implantation of stem cells along with the weak points including rejection and immuno-incompatibility [25]. The method used by this study not to culture the autologous bone marrow derived stem cells but to enrich them by using the centrifuge and to use along with the adipose tissues obtained from the abdomen has a simple process and no rejection as it uses the autologous cells and tissues. It is thought to be a proper treatment method because it can be used in a safe way. The method used 7 cc of autologous bone marrow-derived adult stem cells and 10 cc of adipose tissues, which include 2.4×10^5 adult stem cells and 1.8×10^9 mononuclear cells. These are only 1/50 of the number of adult stem cells required for the osteochondral regeneration, but it was found that these are effective in 90 % or more of the clinical results or imaging results in this study. The mononuclear cells contain the hematopoietic stem cells, endothelial stem cells, and adult stem cells. Some articles reported that some hematopoietic stem cells transdifferentiate into the mesenchymal stem cells and de-differentiate into the osteoblast [26]. This is thought to be because the mononuclear cells also differentiate into the mesenchymal stem cells to influence the regeneration of cartilage.

The scaffold in the stem cells enhances the viability and differentiation of stem cells and provides the frame [27]. The materials used as the scaffold include hyaluronic acid, collagen, fibrin glue, adipose tissues, and platelet-rich plasma. The lipid-filled adipocyte composing the adipose tissues de-differentiate into stem cells or re-differentiate into bones or cartilage, and they can be used as stem cells. Also, they have the homing effect to play the role to move the stem cells to the parts needing them such as the damaged cartilage and facilitate the vascularization to reduce the absorption of adipose tissues. Thus, they can be properly used as the scaffold [28]. This study also used the adipose tissues as the scaffold, and it is judged that they have been helpful to supplement the insufficient number of stem cells and to obtain a clinically excellent result.

The treatment method used in this study is a method which is implemented for the first time. Hence, it is thought that the proper indication needs to be established and that it is not desirable to thoughtlessly use the injection of autologous bone marrow-derived mesenchymal stem cells. The concentration of mesenchymal stem cells gets decreased with age, especially rapidly after 50 years of age, and this needs to be considered. The application of K–L grade IV in high-degree degenerative arthritis needs also to be reconsidered [29, 30]. In addition, as a result of analysis of the cases that showed an inferior result in this study, it is thought that it would be desirable to implement the existing treatment method rather than this operation in the case with accompanying malalignment including the varus deformity of knee joints, the case which is diagnosed to be rheumatoid arthritis, the case when the patient received anti-cancer medication treatment, and so on.

Therefore, the proper indications of the injection of autologous bone marrow mesenchymal stem cells and adipose tissues thought by the authors are the degenerative arthritis of the knee from early to moderate phase (K–L grade I through III), the body mass index (BMI) under 30, the normal alignment or the malalignment with a gradient that can be corrected, the case with no instability, and the case where the patient understands the process of treatment. In addition, it is thought that in the patients with K–L grade I and II, the execution of the injection of BMAC and adipose tissues alone or the execution of the injection along with the arthroscopic debridement according to the condition of knee joints will have excellent effects. Also, in the patients with K–L grade III, it is thought that it will be desirable to execute the injection of BMAC and adipose tissues following the arthroscopic microfracture at the lesion of damaged cartilage. However, in case of the patients with K–L grade IV, it is thought that a better result can be expected by executing the conventional arthroplasty rather than the injection of BMAC and adipose tissues.

This study has some limitations and supplement points. First, the mean age of the subject of this study was 60.7 years old (53 through 80 years old), which was older than the age when the microfracture and the concentration of mesenchymal stem cells are ideal. However, nevertheless this study reported a good result, and from now on, the expansion of the age for the BMAC treatment will be able to be expected. Second, this study evaluated the state of regeneration of cartilage on the basis of the clinical index at the sixth month after the operation and can only judge the results of short-term follow-up. Hence, the additional studies will be needed on the results of long-term follow-up over 5 years after the operation. Third, in order to more objectively judge the results of this injection, it is thought to be needed to execute the MRI of knee joints and the secondary arthroscopy and to perform the biopsy of the regenerated joint tissues at the time of follow-up observation. Finally, in order to improve the efficacy of treatment, it is thought that the studies on how to secure the ideal number of mesenchymal stem cells should be conducted continuously.

Conclusion

As a result of short-term follow-up after the injection of autologous bone marrow mesenchymal stem cells and adipose tissues into the knee joints, superior results were shown including the decrease in pain and the improvement of clinical and functional results of knee joints. For the expansion of indications for this operation and better results, it is thought that the imaging examinations and follow-up arthroscopy should be performed for the objective confirmation of the degree of constant creation and maintenance of cartilage tissues through the long-term follow-up and additional studies and that the technical efforts should be made to secure a greater number of mesenchymal stem cells.

Conflict of interest The authors declare that they have no competing interests.

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