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Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis

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ABSTRACT

Purpose: The aim of the study was to determine if isolated mesenchymal stem cells (MSCs) derived from the infrapatellar fat pad could effectively improve clinical results when percutaneously injected into arthritic knees.
Level of evidence: Therapeutic case–control study; Level III.
Methods: Twenty five stem cell injections combined with arthroscopic debridement were administered to patients with knee OA. A mean of 1.89×10^6 stem cells were prepared with approximately 3.0 mL of platelet-rich plasma (PRP) and injected in the selected knees of patients in the study group.
Results: The mean Lysholm, Tegner activity scale, and VAS scores of patients in the study group improved significantly by the last follow-up visit. No major adverse events related to the injections were observed during the treatment and follow-up periods. The results were compared between the study and control groups, in which the patients had undergone arthroscopic debridement and PRP injection without stem cells. Although the preoperative mean Lysholm, Tegner activity scale, and VAS scores of the study group were significantly poorer than those of the control group, the clinical results at the last follow-up visit were similar and not significantly different between the two groups.
Conclusions: The short-term results of our study are encouraging and demonstrate that infrapatellar fat pad-derived MSC therapy with intraarticular injections is safe, and provides assistance in reducing pain and improving function in patients with knee OA.

1. Introduction

Osteoarthritis (OA) is a cartilage degenerative process involving the immune system, wherein local inflammatory reactions occur with the production of proinflammatory cytokines. Currently, no treatment is available to improve or reverse the process. OA of the knee joint has a particularly significant impact on the affected individual's ability to perform activities of daily living, and combined with the high cost of its management, it poses a major social issue, especially in populations with a long life expectancy [1]. Current treatment options for articular injury and OA itself aim to relieve inflammation and pain, but they do little to delay disease progression [2]. Various surgical methods have been proposed to regenerate articular cartilage, but they all are associated with complications, leaving many patients with inadequately treated cartilage lesions. When left untreated, cartilage lesions can progress to more extensive defects and, ultimately, they may require joint replacement surgery, subject to failure of conservative options. This consequence is the driving force behind numerous ongoing efforts to develop new tissue engineering-based strategies for the treatment of OA [3].

Because of their multilineage potential, immunosuppressive activities, limited immunogenicity, and relative ease of growth in culture, mesenchymal stem cells (MSCs) have attracted attention for clinical use. Although ethical and political issues surround the use of embryonic stem cells, the use of MSCs generally is well accepted by society. Furthermore, MSCs are an autologous source of cells, eliminating concerns regarding rejection and disease transmission, and they are less tumorigenic than their embryonic counterparts [4]. Therefore, MSCs have been suggested for use in the cell-based treatment of cartilage lesions.

In this study, we present the preliminary results (at a minimum of 12 months of follow up) of 25 cases of knee OA treated with intraarticular injections of autologous MSCs. Autologous MSCs were separated from the infrapatellar fat pad of OA patients, isolated in vitro, and then injected into the patients' knee joints. The aim of the study was to determine whether isolated MSCs derived from the infrapatellar fat pad are safe and can effectively improve clinical results when percutaneously injected into arthritic knees.

2. Patients and methods

2.1. Patients

Between January 2010 and September 2010, 25 stem cell injections combined with arthroscopic debridement were administered

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to patients with knee OA (Table 1). The study group comprised 8 men and 17 women, with an average age of 54.1 (range, 34–69) years. Eligible patients were aged ≥30 years with idiopathic or secondary knee OA. The mean follow-up period was 16.4 months (range, 12–18) months.

The exclusion criteria were inflammatory or postinfectious arthritis, previous arthroscopic treatment for knee OA, varus or valgus deformity of 5° or more, previous major knee trauma, Kellgren–Lawrence grade 4 OA as defined by the modified Kellgren–Lawrence classification [5] in 2 compartments (the medial or lateral compartments of the tibiofemoral joint or the patellofemoral compartment), persons over 70 years of age, intraarticular corticosteroid injection in the preceding 3 months, a major neurologic deficit, serious medical illness (life expectancy of <2 years or a high intraoperative risk), and pregnancy. Patients were also excluded if they had large meniscal tears ("bucket handle" tears), were unable to provide informed consent, or were deemed unlikely to comply with follow up. All the patients provided written informed consent according to regulations, after approval of the ethics committee, and they were operated by the same surgeon (the first author).

2.2. Arthroscopic procedure and clinical assessment

The patients received arthroscopic treatment under spinal anesthesia, with the use of a tourniquet. The orthopedic surgeon evaluated the medial, lateral, and patellofemoral joint compartments, graded articular lesions according to the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package, irrigated the compartment with at least 1 L of saline, and performed one or more of the following treatments: synovectomy; debridement; or excision of degenerative tears of the menisci, fragments of articular cartilage, chondral flaps, or osteophytes that prevented full extension. Abrasion or microfracture of chondral defects was not performed.

Clinical assessment was performed retrospectively using the arthroscopic surgery database, medical records, and telephone interviews. The clinical outcome was evaluated using the Lysholm score [6], Tegner activity scale [7], and visual analog scale (VAS) for grading knee pain. On the 10-mm VAS, scores (0–10) for pain (0 = no pain; 10 = worst possible pain) [8] were recorded. Patients were evaluated preoperatively, 3 months postoperatively, and at the last follow-up visit (average, 16.4 months; range, 12–18 months). Radiographic evaluation included the standing weight-bearing anteroposterior view, lateral view, skyline view, and full-length anteroposterior view.

2.3. Sample collection and MSC isolation

For 1 week before the infrapatellar fat pad harvesting procedure, the patients were restricted from consuming corticosteroids or nonsteroidal anti-inflammatory drugs. After arthroscopic surgery, we collected the fat pad immediately, followed by arthroscopic surgery. The adipose synovium was harvested from the inner side of the infrapatellar fat pad by extension of the skin incision at the arthroscopic lateral portal site (Fig. 1). Then, the infrapatellar fat pad was collected (average weight, 9.4 g; range, 6.9–11.2 g). The MSCs derived from the infrapatellar fat pad were isolated as described previously [9,10]. Briefly, the pad was minced and washed extensively with phosphate-buffered saline and an equal volume of 0.1% collagenase type 1 (Worthington Biochemical Corporation, Lakewood, NJ). The tissue was placed in a rotary incubator at 37 °C, with continuous agitation for 3 h. After digestion, the lipoaspirates were centrifuged at $1200 \times g$ for 10 min to separate the lipoaspirate and the collagenase. The lipoaspirates were then washed 3 times to remove any remaining collagenase. After the last round of centrifugation, cells in the aspirates were counted using a hemocytometer. Before injection, bacteriologic tests were performed on the samples (to ensure the absence of contamination), and the viability of the cells was assessed using the methylene blue dye exclusion test.

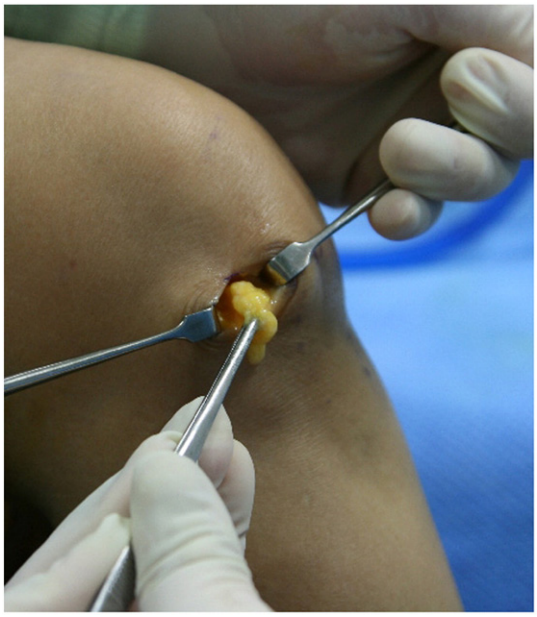

Fig. 1. Adipose synovium was harvested from the inner side of the infrapatellar fat pad by skin incision extension of the arthroscopic lateral portal site.

Table 1
Overview of the different patient groups.

	Study group	Control group	*P* value[a]
	Mean ± SD	Mean ± SD	(95% CI)
Age	54.2 ± 9.3	54.4 ± 11.3	0.67 (−7.1–4.65)
Follow-up (M)	16.4 ± 2.3	17.2 ± 1.8	0.23 (−1.9–0.46)
ICRS cartilage (Grade)	3.7 ± 0.4	2.8 ± 0.8	<0.001 (0.19–1.08)
Kellgre–Lawrence (Grade)	3.3 ± 0.8	2.7 ± 0.7	0.005 (0.63–1.37)
Sex M/F	8/17	8/17	

CI = confidence interval.
[a] The independent *t*-test.

2.4. Injection of MSCs

Because the preparation of stem cells takes 3 or 4 h, the first injection time of the stem cells was the same day as the arthroscopic operation. After the stem cells were isolated, a mean of 1.89×10^6 (range, $1.2–2.3 \times 10^6$) stem cells were prepared with approximately 3.0 mL of platelet-rich plasma (PRP) and injected in the selected knees of patients in the study group. The skin was dressed under aseptic conditions, and the injection was performed through a classic lateral approach of the upper pole of the patella using a 22-g needle. Before injection, the knee first was aspirated for hemarthrosis, and no steroid was injected in the knee joint. All injections were done in an outpatient setting. At the end of the procedure, the patient was invited to bend and extend the knee a few times, in order to allow the stem cells with PRP distribute throughout the joint before becoming a gel. After the injection, the patients were sent home to use cold therapy/ice on the affected area for pain.

During the treatment period, we did not restrict walking, and rest or mild activities (such as exercise biking, mild exercises in a pool) were indicated. Subsequently, the gradual resumption of normal sport or recreational activities was allowed, as tolerated. No analgesics, anti-inflammatory drugs, or immunosuppressive drugs were administered or allowed after the procedure. After the first injection with stem cells and PRP, 3 mL of PRP was administered every 7 days as the second and third rounds of treatment.

2.5. PRP preparation

For PRP preparation, a 60-mL venous blood sample (collected in a bag containing 4 mL of sodium citrate) was collected for every lesion treated. The complete peripheral blood count was determined using the first blood sample collected. Then, the samples were centrifuged twice (at 1800 rpm for 15 min to separate the erythrocytes, and then at 3500 rpm for 10 min to concentrate the platelets) to yield 6 mL of PRP. The PRP was divided into 2 units of 3 mL each. One unit was sent to the laboratory for analysis of platelet concentration and quality testing (bacteriologic tests), while the other was used for the first injection within 2 h of preparation.

The total number of platelets per microliter in the PRP was a mean of 500% times greater than that in the whole blood, and an average of 1,280,000/μL platelets were administered at the lesion sites during every injection. For the second and third rounds of treatment, PRP injections were administered every 7 days. Before all injections, calcium chloride was added to the PRP unit to activate the platelets. All the procedures were performed in the same laboratory setting, and all open procedures were performed in an A-class sterile hood.

2.6. Control group treatment

For comparison of the clinical results, a control group that matched the study group in terms of patient age and sex and follow-up period was selected from over 500 patients who also had undergone arthroscopic debridement accompanied by postoperative PRP injections between January and September 2010. The selection process was aided by computerized randomization, and the matched-group analysis was performed retrospectively. The group comprised eight men and 17 women, with an average age of 54.4 (range, 36–69) years. On the operative day, PRP was prepared at a mean volume of 3.0 mL and injected without stem cells into the selected knees of the control patients. Then, similar to the study group, the control group was administered PRP without stem cells at 1-week intervals as the second and third rounds of treatment. The other factors (arthroscopic procedure and postoperative rehabilitation) were the same as those for the study patients.

2.7. Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Studies (SPSS) software, version 12.0, for Windows (IBM Corporation, Armonk, NY). The clinical scores were given as the mean (SD) at three time points: preoperatively, 3 months postoperatively, and at the last postoperative follow-up visit. We checked the normality of distribution by using the Shapiro–Wilk test. This research followed normal distribution because the probability of the Shapiro–Wilk test was $P>0.05$ and the number of patients was 25 in each group. The paired t-test was used for the within group analysis (pre-op. vs post-op in the same group) and the independent t-test was used for between group analysis (study group vs control group). The level of significance was $P<0.05$.

3. Results

No major adverse events related to the injections were observed during the treatment and follow-up periods, except for 1 case, in which the patient experienced marked pain with swelling after the injection, which resolved spontaneously after 2 weeks. In some cases, slight pain was experienced in the first 2 or 3 days after the injection. A statistically significant improvement from the baseline was noted for all the clinical scores at both the 3-month follow-up visit and the last follow-up visit. No patient was lost to follow up; however, 4 patients were not available for examination in the outpatient clinic, but they were contacted by telephone, and they answered the questionnaire for clinical score.

The mean Lysholm, Tegner activity scale, and VAS scores of patients in the study group improved significantly ($P<0.001$) by the last follow-up visit (Table 2). After the operation, 23 patients (92%) showed an improved Lysholm score, 1 patient's (4%) score did not change, and 1 patient's (4%) score worsened. The Tegner activity score postoperatively improved for 19 patients (76%), remained unchanged for 5 patients (20%), and worsened for 1 patient (4%). The VAS was used to assess patients' pain both pre- and postoperatively. After the operation, 21 patients (84%) reported pain reduction, 1 patient (4%) reported no change, and 3 patients (12%) reported an increase in pain.

Table 2
Clinical results of the different patient groups.

	Study group	Control group	P value[a]
	Mean ± SD	Mean ± SD	(95% CI)
Lysholm score			
Preop	41.2 ± 12.4	50.0 ± 11.1	0.01 (−15.50–−2.10)
Last F/U	68.1 ± 18.5	69.4 ± 20.4	0.81 (−12.40–9.76)
Tegner activity scale			
Preop	1.5 ± 0.5	2.1 ± 0.8	0.003 (−0.99–−0.21)
Last F/U	2.8 ± 1.2	2.9 ± 1.0	0.71 (−0.75–0.51)
VAS			
Preop	4.9 ± 1.2	3.9 ± 1.0	0.001 (0.42–1.66)
Last F/U	2.7 ± 1.8	2.2 ± 1.7	0.34 (−0.52–1.48)

CI = confidence interval.
[a] The independent t-test.

To establish the indications for our treatment, we determined the parameters that influenced the clinical outcome. We found that an increased VAS score and a decreased Tegner activity scale score in older patients (>55 years) at the last follow-up visit (VAS, $P=0.007$; Tegner activity scale, $P=0.049$). This implies that MSC therapy was more effective in younger patients. Furthermore, we found that patients with OA of ICRS grade 3 on the VAS showed greater improvement than those with OA of ICRS grade 4 ($P=0.024$).

To analyze the outcome of our stem cell therapy, the results were compared between the study and control groups, in which the patients had undergone arthroscopic debridement and PRP injection without stem cells. In the control group, the mean Lysholm, Tegner activity scale, and VAS scores improved significantly ($P<0.001$) by the last follow-up visit. Although the preoperative mean Lysholm, Tegner activity scale, and VAS scores of the study group were significantly poorer than those of the control group ($P<0.001$), the clinical results at the last follow-up visit were similar and not significantly different between the 2 groups (Lysholm score, $P=0.812$; Tegner activity scale, $P=0.706$; VAS, $P=0.338$) (Figs. 2–4). However, the degree of improvement was superior in the study group, which had received stem cell injections. Although the scores of the study group tended to improve to a great degree by the last follow-up visit, the difference between the study and control groups was not significant (Lysholm score, $P=0.169$; Tegner activity scale, $P=0.133$; VAS, $P=0.261$), 95% confidence interval (Lysholm score, −3.3–18.3; Tegner activity scale, −0.15–1.11; VAS, −1.55–0.43). The average Lysholm score increased 26.9 points by the last follow-up visit in the study group, whereas it increased only 19.4 points in the control group (Fig. 5). The average Tegner activity scale score increased 1.3 points by the last follow-up visit in the study group, but it increased only 0.8 points in the control group. Finally, the average VAS score decreased 2.2 points by the last follow-up visit in the study group, while it decreased 1.7 points in the control group.

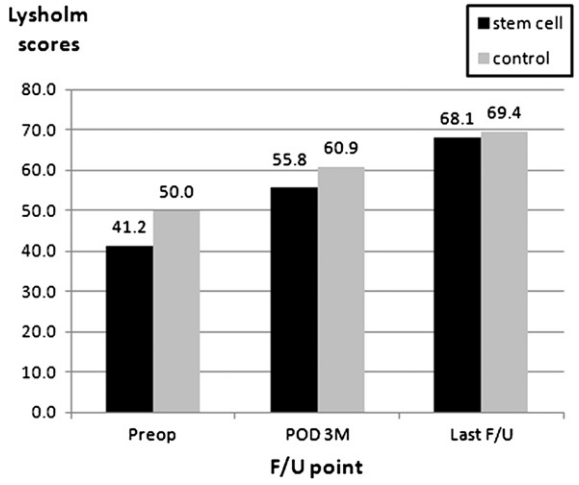

Fig. 2. Bar graph showing the Lysholm scores preoperatively, at the 3-month follow-up visit, and at the last follow-up visit. Study group = stem cells + PRP injection; control group = PRP injection.

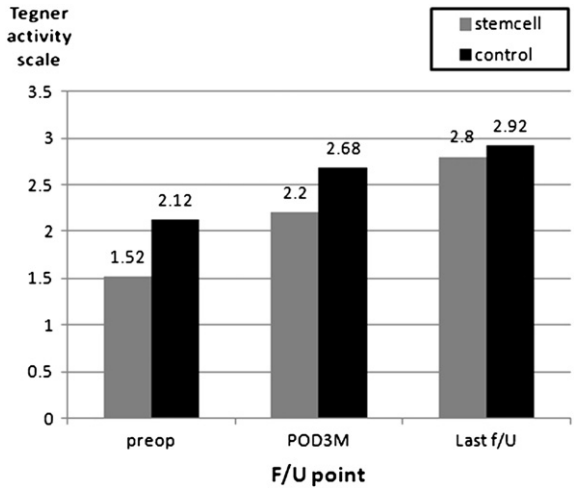

Fig. 3. Bar graph showing the Tegner activity scale preoperatively, at the 3-month follow-up visit, and at the last follow-up visit. Study group = stem cells + PRP injection; control group = PRP injection.

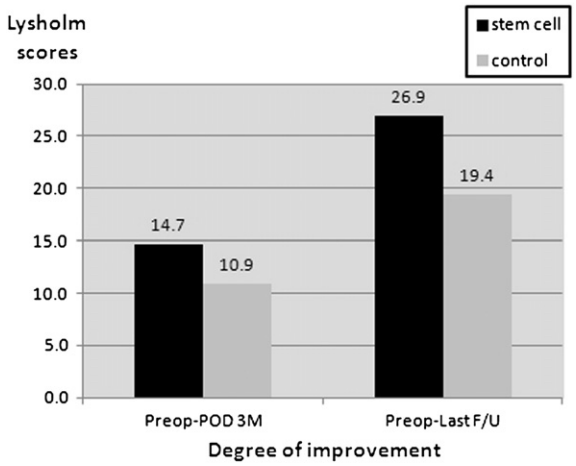

Fig. 5. Bar graph showing the degree of improvement, according to Lysholm score, preoperatively to the 3-month follow-up visit, and preoperatively to the last follow-up visit. Study group = stem cells + PRP injection; control group = PRP injection.

4. Discussion

The first aim of this study using MSCs was to evaluate the safety of our technique. No complications such as infection, marked muscle atrophy, fever, hematoma, tissue hypertrophy, adhesion formation, or other major adverse events occurred among the study subjects. The secondary aim was to analyze the effectiveness and application modalities for use in further studies: we found that the MSC therapy provides assistance in reducing pain and improving function in patients with knee OA.

Cartilage defects have a very limited intrinsic healing capacity. Small defects can spontaneously undergo repair with the production of hyaline cartilage, but large defects undergo repair only with the production of fibrous tissue or fibrocartilage, which are biochemically and biomechanically different from normal hyaline cartilage. Therefore, degeneration occurs subsequently and can progress to osteoarthritic changes in some cases [11].

Recently, MSCs have been suggested for use in the cell-based treatment of cartilage lesions. Chondrogenesis of MSCs was first reported by Ashton and colleagues [12], and a defined medium for the in vitro chondrogenesis of MSCs was first described by Johnstone and colleagues [13], who used micromass culture with transforming growth factor-beta (TGF-β) and dexamethasone. With regard to in vivo studies, the transplantation of MSCs into full thickness articular cartilage defects has been attempted under various conditions. Although many studies have been successful, several questions still persist that limit the clinical application of these cells for cartilage injury, such as from which tissue are suitable MSCs derived or what conditions are appropriate for cartilage repair.

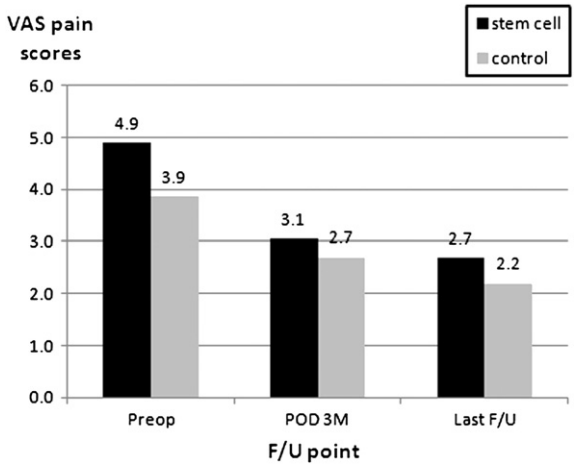

Fig. 4. Bar graph showing the visual analog scale pain scores preoperatively, at the 3-month follow-up visit, and at the last follow-up visit. Study group = stem cells + PRP injection; control group = PRP injection.

Currently, very few clinical studies on MSC transplantation for cartilage repair have been reported, though animal experiments on MSC use in the prevention and treatment of experimental OA have showed encouraging results [14,15]. In 2 reports, experiments on humans [16,17] involving the intraarticular injection of autologous MSCs yielded good results after 6 months. In 2008, Centeno and colleagues reported the use of autologous culture-expanded bone marrow-derived stem cells for knee cartilage regeneration in humans [17]. In their study, the patients' pain, as determined by the VAS, and range of motion improved, and MRI showed significant articular cartilage growth and meniscus regeneration. Currently, only one prospective clinical study on MSC transplantation for cartilage repair has been published; in this study, bone marrow-derived MSCs were resuspended in a collagen type I gel and transplanted with an autologous periosteal flap [18]. Patients with knee OA who had undergone high-tibial osteotomy were treated using a cell-containing scaffold with the periosteal flap transplanted into a cartilage defect in the medial femoral condyle, and their outcomes were compared with those of patients in whom a cell-free scaffold with the periosteal flap was transplanted into similar lesions. Although the cell-treated group showed no significant clinical improvements compared with the control group, the arthroscopic and histologic scores were better in the MSC-transplanted group.

As mentioned above, previous reports were almost entire case reports on a few patients, while our study is a study including many patients. Although this is a retrospective study, the results prove that stem cell therapy is safe, and provides assistance in the treatment of knee OA. Although the preoperative status of the study group was poorer than that of the control group, the clinical results at the last follow-up visit were similar. In addition, the degree of improvement from the preoperative status was greater in the study group than in the control group.

Although our technique is primitive, we tried to select a technique that was substantially better than those reported previously on stem cell therapy for knee OA. To obtain good results, the source of the MSCs is very important. The choice of the stem cell source is determined by the ease of harvesting, population density, and differentiation potential of the cells, as their abilities vary among different

tissue sources [19]. Bone marrow- and synovium-derived MSCs have shown good results [19], and we intend to concentrate on these two sources. Bone marrow-derived stem cells have been widely studied, and there is a wealth of information in the literature concerning them [20]. To date, only limited reports have been published on human autologous bone marrow stromal cell implantation for cartilage repair [21,22]. Unfortunately, bone marrow harvesting is painful and is associated with donor site morbidities and risks of wound infection and sepsis [23]. Furthermore, with increasing age, there is a decrease in the MSC numbers [24], lifespan, and proliferation [25] and differentiation potentials [26]. Therefore, an alternative cell source that is easy to obtain, has a low risk of complications, and has a high yield of cells with good proliferation and differentiation potentials that do not decline with age is ideal for enabling optimal cell-based tissue repair therapies in an aging population.

In this respect, MSCs extracted from the infrapatellar fat pad have been induced to exhibit the chondrogenic, adipogenic, and osteogenic phenotypes by using appropriate media [27]. These cells have been shown to maintain their differentiation potential even in the later stages of life [28], and they may have better chondrogenic potential compared to the bone marrow-derived MSCs [19]. In addition, compared with the bone marrow, the infrapatellar fat pad is reported to give a higher yield of adherent colony-forming cells: A 30-mL bone marrow aspirate afforded approximately 1×10^5 cells [29], whereas 21 mL of infrapatellar fat pad yielded approximately 5.5×10^6 cells [27]. Obtaining a large number of cells at harvest has the advantage of reducing the need for costly and time-consuming tissue culture expansion, which is also associated with the risk of contamination. Moreover, the pain and morbidity associated with the harvesting of infrapatellar fat pad cells are considerably less than that associated with bone marrow cell harvesting [27].

Although we collected an average of just 9.4 g of infrapatellar fat pad in the present study, we could extract an average of 1.89×10^6 stem cells. Sekiya compared the MSCs derived from bone marrow, synovium, periosteum, adipose tissue, and muscle and showed that the synovium was the best source of MSCs for use in cartilage regeneration: synovium-derived MSCs had a greater proliferative capacity and chondrogenic potential [19]. An important consideration in tissue engineering is harvesting the greatest number of MSCs with the highest potential. In this regard, the adipose synovium cells have an advantage because of their high chondrogenic potential and accessibility; sufficient amounts of adipose synovium can be harvested with possibly fewer complications. Thus, we chose the infrapatellar fat pad as a source of MSCs for use in cartilage defect treatment. In addition, the infrapatellar fat pad frequently is resected during arthroscopy or total knee arthroplasty for improved surgical visualization and for the treatment of chronic impingement and fiduring of the fat pad (Hoffa's disease) [30]. No long-term adverse effects have been noted following its resection [31]. Even in our study, no adverse effects of infrapatellar fat pad harvesting were noted.

In the present study, we administered injections of patients' stem cells prepared with PRP because PRP is a novel biological scaffold that has been widely used as an MSC carrier for clinical chondrogenesis. PRP is nonimmunogenic, bioabsorbable, and can be easily prepared preoperatively. According to Frechette and colleagues, the platelet augmentation approach is based on the concept that platelets contain key growth factors such as platelet-derived growth factors, TGFs, and various interleukins [32]. They hypothesize that the released growth factors have chemotactic and mitogenic effects on MSCs and osteoblasts when applied to bony tissues [33]. In fact, recent research has reported that treatment with PRP injections is safe and has the potential to reduce pain and improve knee function and quality of life in patients with degenerative osteoarthritic knees [34]. Because the average baseline blood platelet count in an individual is $200{,}000\pm75{,}000/\mu L$, a platelet count of 1,000,000/μL (5-fold greater than the average) commonly is described for therapeutic platelet-rich preparations [35]. In our study, we administered an average of 1,280,000/μL in the patients' knees at every injection.

In this study, we did not culture stem cells but isolated them from the infrapatellar fat pad, and then injected into patients' knees. The number of MSCs that can be isolated from the infrapatellar fat pad is fairly limited. Therefore, most research on cartilage regeneration has focused on the use of culture-expanded cells [36–39]. Various elements of the local microenvironment during culture can affect MSC differentiation [40–44], and culture expansion carries some risk of infection or changes in MSC properties, however; thus, we just isolated stem cells from the infrapatellar fat pad and injected them into the patients' knees. Although the technique of this study was primitive, we obtained good results in the study group at a minimum follow-up period of 1 year, probably because of the paracrine effects of the injected stem cells. It is widely known that stem cell therapy has two main mechanisms of action. The first is that these cells comprise the final tissue in human organs. The second mechanism, the most convincingly proven so far, is the paracrine effects of the cytokines and growth factors released by the grafted cells, which favorably influence the microenvironment by triggering host-associated signaling pathways [45] and lead to increased angiogenesis, decreased apoptosis, and possibly, induction of endogenous generation.

The primary objective of our study was to evaluate the safety of our technique. No complications such as infection, marked muscle atrophy, fever, hematoma, tissue hypertrophy, adhesion formation, or other major adverse events occurred among the study subjects. Only minor adverse events were detected, such as a mild pain reaction and effusion after the injections, which persisted for not more than 2 days. The secondary aim was to analyze the indication criteria and application modalities for use in further studies. In our study, better results were achieved in younger patients, which was expected and easily explained by the high percentage of living and vital cells in the knee joint of younger patients. Therefore, a high response potential to the paracrine effects was expected. At the last follow-up visit, the results were poorer in patients with a higher cartilage grade. Thus, good results are obtained with stem cell therapy of knee OA in young patients and those with early cartilage degeneration.

The present study does have some limitations. The first problem with our stem cell therapy is that the number of cells to be injected to achieve the optimal response is unknown. Second, it is unknown whether a single injection is adequate or >1 injection within a time period is necessary to obtain the desired result. Third, we need more experience on a large scale to determine the proper use of costimulators. The other important limitations of our study are that we do not have data on the effects of pure stem cell injections, and it is difficult to distinguish the effects of the stem cells from those of the PRP. Lastly, the number of subjects was small, the follow-up period was short, the data were collected retrospectively, and neither a routine second-look arthroscopy nor an MRI examination was performed.

In the future, tissue-engineering techniques hold promise for repairing damaged cartilage within joints. Several challenges still need to be overcome, however, which include identifying the optimal source of stem cells, scaffolds, and growth factors. Nonetheless, this study proposes a new option for the treatment of knee OA. The positive clinical outcomes obtained support further randomized controlled clinical trials of this treatment modality with a large number of patients and a long follow-up period.

5. Conclusions

The short-term results of our study are encouraging and demonstrate that infrapatellar fat pad-derived MSC therapy with intraarticular injections is safe, and provides assistance in reducing pain and improving function in patients with knee OA. However, before MSC

therapy can be widely adopted as a new method for the treatment of knee OA, the techniques involved should be improved.

Conflict of interest

None.

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