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ORIGINAL ARTICLE

Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis

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Abstract The aims of this study were to analyze the range of cartilage damage and patellofemoral joint (PFJ) degeneration in degenerative osteoarthritis (OA) and determine the duration for the positive effects of platelet-rich plasma (PRP) injection. This study included 65 patients suffering from OA that were treated with intra-articular PRP injection. The patients were prospectively evaluated at 1, 3, 6, 9, and 12 months after the procedure using a visual analogue scale (VAS) score and an International Knee Documentation Committee (IKDC) score. Clinical improvement in the average VAS score from 7.4 before the procedure to 4.2 at 6 months post-procedure had been reported, but the symptoms tended to deteriorate to 5.0 1 year after injection. The IKDC score also showed statistical significance ($P < 0.05$). Patients reported relapsed pain 8.8 months after the procedure. Developing degeneration according to the Kellgren–Lawrence grade reduced the clinical effects of PRP ($P < 0.05$) and also accelerated the time for feeling relapsed pain ($P < 0.05$). There was a statistically significant negative correlation between patient age and the PRP potential in the VAS score (slope = 0.1667) and IKDC score (slope = 1.3333). The presence of PFJ degeneration is expected to produce a worse outcome ($P < 0.05$). While intra-articular PRP injection can be used for the treatment of early OA, increasing age, and developing degeneration result in a decreased potential for PRP injection therapy.

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Introduction

As the average human lifespan increases, there is an increased chance of cartilage damage that causes patient pain. This in turn will contribute to a decrease in the quality of life for elders that result in poor socioeconomic effects. In addition, symptomatic cartilage lesions can cause significant morbidity as articular cartilage tissues have limited healing potency [1–3]. Although hyaline cartilage is well known for its smooth surface and excellent ability to withstand huge amounts of pressure, the regenerative ability of cartilage tissue is poor with increasing age [4].

In the past several decades, the major treatment for severe degenerative osteoarthritis (OA) has been to replace the articular surfaces. In cases of early OA, the major treatment option is a conservative therapy for pain reduction because there is nothing known to stop the progression of degeneration sequences. Although joint replacement treatment has developed significantly from technical point of view, it is still insignificant when viewed from a regenerative perspective. Recently, new reparative methods, including platelet-rich plasma (PRP) treatment, to treat early OA and cartilage lesions are getting clinical attention. PRP consists of a volume of plasma with a platelet concentration above baseline values that are obtained from the patient's own blood [5]. As such, PRP is safe from immune reaction and blood diseases because it is obtained from autologous blood and the application of PRP in the outpatient clinic is possible. In addition, it is cheap and effective, and no additional procedures are required [6, 7]. Many studies with PRP have shown positive

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clinical results. In a recent study, the effectiveness of PRP treatment for early OA in young patients with low BMIs was reported which showed that PRP treatment was more effective than hyaluronic acid intra-articular injections [8, 9].

The goals of this study were to differentiate results according to the range of cartilage damage and patellofemoral joint (PFJ) degeneration and to clarify the period of PRP therapy positive effects.

Materials and methods

Study design and patient selection

This was a non-randomized prospective study. Each patient was diagnosed with degenerative OA by a detailed clinical history of knee pain, a complete physical examination, laboratory test results, and radiologic findings (X-ray or MRI). The usual presenting symptoms were knee pain involving one or both knee joints, mild-to-moderate activity impairment, and joint stiffness and swelling. A neurological evaluation was also performed to determine the possibility for radiculopathy. Three views of the knees were obtained for each patient: the posteroanterior weight-bearing in full extension, the lateral view for checking tibiofemoral joint space degeneration, and the knee tangential (Merchant) view for PFJ degeneration. The objective evidence for OA provided by radiographs was as follows: the presence of joint space narrowing, osteophyte (bony spur) formation, pseudocysts in the subchondral bone, and increased density of the subchondral bone. A single reader scored all the films and classified them according to the Kellgren–Lawrence criteria [10]. Patients were not excluded in the absence of significant radiographic findings but were interpreted as a possible sign of early OA.

Patients with other underlying diseases including rheumatoid arthritis (RA), gout, ankylosing spondylitis (AS), infectious joint disease, radiculopathy from spinal disease, acute knee joint injury, and secondary OS were excluded from the study. Exclusive criteria included platelet dysfunction syndrome, critical thrombocytopenia ($<10^5$/mL), hypofibrinogenemia, septicemia, coagulopathies, presence of tumors or metastasis, active infection, pregnancy or breast-feeding, and immune deficiencies. Patients taking non-steroidal anti-inflammatory drugs (NSAIDs) were asked to stop taking the medication for 2 weeks prior to PRP injection. We did not inject PRP into the knee joints of patients who had advanced degenerative OA as assessed by radiologic findings with a Kellgren–Lawrence grade IV because we believe operative therapies such as joint replacement arthroplasty are preferred in severe OS cases. Patients completed a clinical result questionnaire prior to the procedure. Informed consent was obtained from all patients.

Between December 2008 and August 2010, 65 patients suffering from degenerative OA were enrolled in our prospective database. They were treated with a single PRP intra-articular injection. They were prospectively evaluated at 1, 3, 6, 9, and 12 months after the procedure. The mean follow-up period was 19.8 months (range 12–36 months). All patients in the study were assessed during the follow-up period without follow-up loss. In total, 12 male (18.5%) and 53 female (81.5%) patients were evaluated with a mean age of 59.7 years (range 32–85 years). Forty patients (61.5%) were treated unilaterally, whereas 25 patients were treated bilaterally for a total of 90 knees. Three patients had experience with hyaluronic acid intra-articular injection treatment before the PRP intra-articular injection of this study. The radiologic findings were categorized as follows: 38 knees (42.2%), Kellgren–Lawrence (KL) grade I degenerative OA; 29 knees (32.2%), KL grade II; and 15 knees (16.7%), KL grade III. We considered KL grade I as mild OA, KL grade II as mild–moderate OA, and KL grade III as moderate OA. There were 54 knees (60%) that had PFJ degeneration (Table 1).

Platelet-rich plasma preparation

We collected 54 mL of venous blood from each patient's arms or legs with 18-gauge needled syringes to minimize

Table 1 Characteristics of age, sex, and injection site according to KL criteria

	Kellgren–Lawrence grade			*P* value
	I ($n = 38$), mild	II ($n = 36$), mild–moderate	III ($n = 16$), moderate	
Age	57.05 ± 9.42	60.81 ± 10.95	63.38 ± 9.32	0.079
Sex				
F	32 (84.2)	30 (83.3)	13 (81.3)	0.965
M	6 (15.8)	6 (16.7)	3 (18.7)	
Injection site				
Lt.	18 (47.4)	18 (50.0)	8 (50.0)	0.970
Rt.	20 (52.6)	18 (50.0)	8 (50.0)	

Mean ± SD, Number (%)

platelet damage during blood sampling. A 6 mL aliquot of anticoagulant citrate dextrose-A (ACD-A) was mixed to the gathered blood to prevent the coagulation cascade. We prepared the PRP using a Magellan® Autologous Platelet Separator (Medtronic Biologic Therapeutics and Diagnostics, Minneapolis, USA) system and the corresponding kits to produce 6 mL PRP. The process began when the collected blood was loaded into the specially designed disposable syringes. If the patient needed a larger volume of PRP, the blood gathering and centrifugation was repeated as the syringes can be reused up to 3 times in the same patient. All procedures were performed under sterile conditions. The PRP was then loaded to the syringe automatically. Platelet activation was not used because we thought that the slow emission of growth factors embedded in the platelet alpha-granules that contacted local tissues at the injection site was more effective.

Injection procedure

Our study was based in the outpatient department. The skin dressing was sterilely conducted with a wide enough area to palpate the patella with gloved hands. The injection site was approached superolaterally using a 23-gauge needle under the supine position. We used 3 mL of PRP in each knee joint. Mild pain occurred occasionally during injection. After all these procedures, a small bandage was applied at the injection site without compression. A single person executed all of the procedures.

Post-procedure management and follow-up

The patients went home on the same day as treatment with the following instructions. The intake of specific medicines such as NSAIDs was to be limited with the understanding for the possibility of mild pain or swelling on the knee for 2 weeks after injection. Patients were permitted to continue with daily living activities immediately, but were limited for extensive use of their knees for several days. In addition, we recommended the patients to see their physician in any situation of uncomfortable sensation. Bandages were removed at day 2 post-procedure. All patient complaints and complications were recorded. Post-injection assessments were planned at 1, 3, 6, 9, and 12 months after the injection. Clinical results were evaluated using International Knee Documentation Committee (IKDC) scoring and the visual analogue scale (VAS) score. The VAS for pain was scored in a linear fashion from 0 (no pain) to 10 (worst pain ever experienced). Patients were asked to rate their pain according to the score system at every follow-up visit. The IKDC score consisted of several questionnaires to assess the function of the affected knees.

We recorded the time when each patient started to experience relapse pain. Any other procedures or treatments were not performed during our follow-up period.

Statistical analysis

Statistical analyses were conducted using the SPSS program (Statistical Package of Social Sciences, Chicago, IL, USA) for windows operation system version 18.0. A 95% confidence interval (CI) was applied to the averages. A P value less than 0.05 was considered statistically significant. The results were described as the mean ± standard deviation (SD). The repeat measured ANOVA test, paired t test, chi-square test, and the simple regression analysis were used to analyze correlations between factors.

Results

Overall, the average VAS score improved from 7.4 before the procedure to 5.0, 4.5, and 4.2 for 1, 3, and 6 months after procedure, respectively. However, the clinical symptoms tended to deteriorate to 4.7 and 5.0 for 9 months and 1 year, respectively (Fig. 1).

On average, patients felt relapsed knee pain 8.8 months after the procedure. In the KL grade I group, the mean VAS score changed consistently from 7.3 before the procedure to 3.3 after 6 months, and rose again to 4.0 after 1 year. The start time for relapsing pain was 9.9 months after injection. In the KL grade II group, the average VAS score changed from 7.4 before the procedure to 4.4 at 6 months follow-up and tended to increase in pain to 5.3 at 1 year post-treatment. The period of pain relief was 9.0 months. In the KL grade III group, a decreased VAS score was

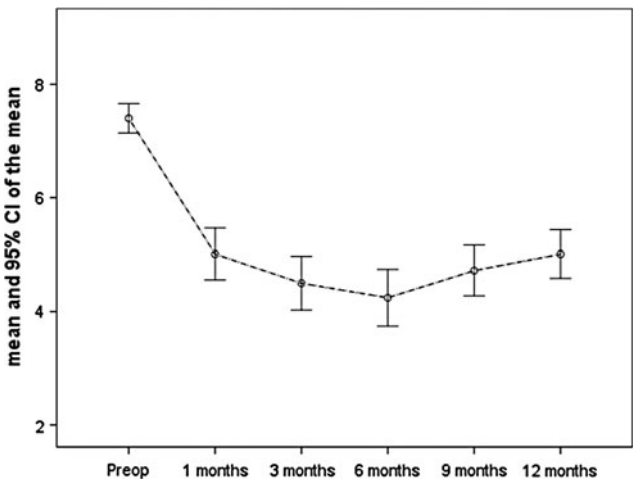

Fig. 1 Change of VAS score. The VAS score changed with a V-shaped appearance

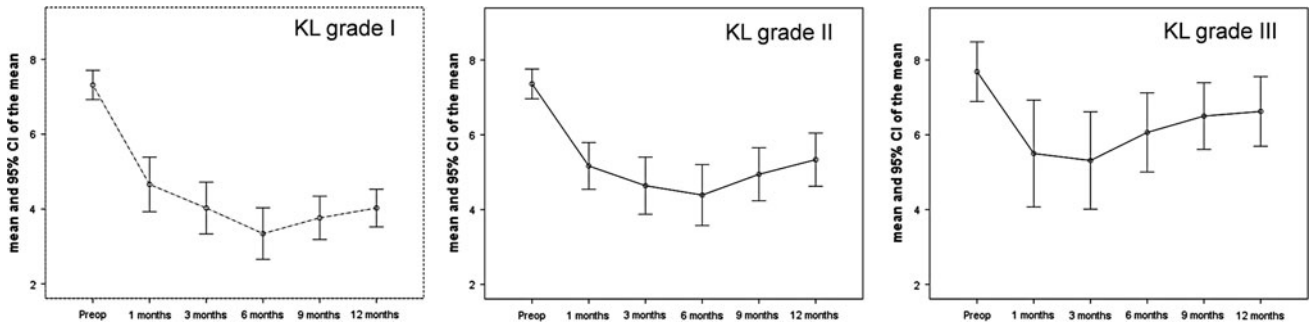

Fig. 2 Change of VAS score according to KL grade. Early OA showed a more significant improvement and long-lasting effect of PRP treatment ($P < 0.05$)

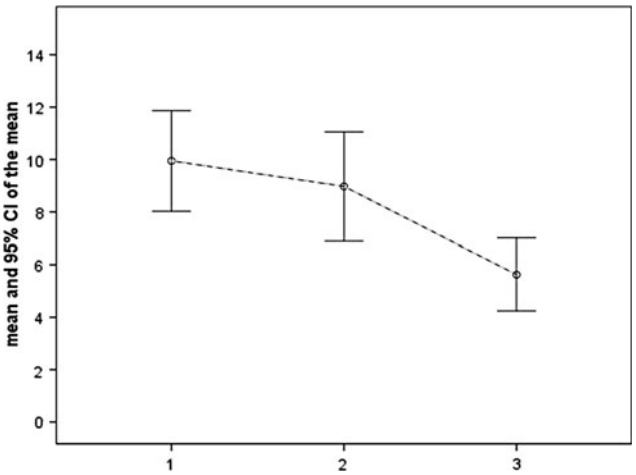

Fig. 3 The time of relapsing pain and KL grade. KL grade I group showed a long-lasting effect of PRP treatment relative to KL grade III with statistical significance ($P < 0.05$). There was no statistical significance between KL grades I/II and II/III

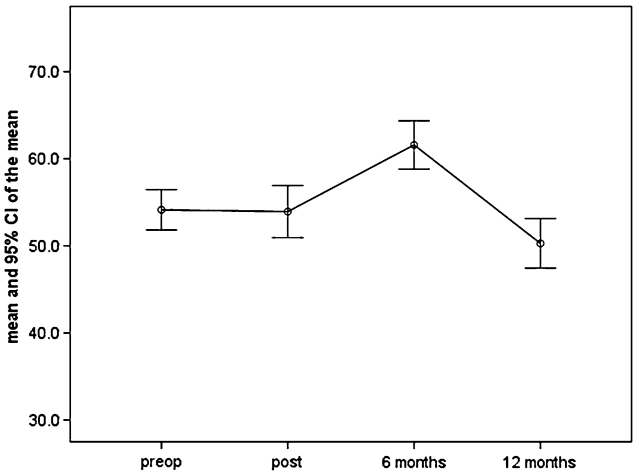

Fig. 4 Change of IKDC score. IKDC score showed clinical improvement and deterioration as time progressed

reported from 7.7 before the procedure to 5.3 at 3 months post-treatment; however, the score was reported as 6.1 at 6 months post-treatment. Relapsing pain was only detected at 5.6 months (Fig. 2). The relationship between KL grade and the time of relapse pain was analyzed using a repeated measures ANOVA test and was found to be statistically significant ($P = 0.037$). There was a shortened time to the re-onset of pain according to KL grade (Fig. 3). When using a repeated measures ANOVA test between VAS score and KL grade, the clinical effects showed a decreased tendency between KL grades I and III ($P = 0.017$). However, there was no significant difference between KL grades I and II, and KL grades II and III.

The IKDC score showed nearly the same results. The mean IKDC score changed from 54.1 before the procedure to 53.9 at 1 month post-procedure, 61.6 at 6 months post-procedure, and 50.3 at 1 year post-procedure. Clinical results of PRP injection were again deteriorated (Fig. 4), and we classified the results based on degeneration. In the KL grade I group, the IKDC score improved from an initial score of 64.6–67.4 at 6 months after the procedure, but deteriorated to 60.9 at the 1-year follow-up. There was a temporally deteriorated phase at 1 month after injection (IKDC score was 60.7). In the KL grade II group, the IKDC score showed a steady improvement from an initial value of 50.1 to 59.7 at 6 months after treatment. The worst score in this group was at 1 year post-treatment at 44.8 at 1 year. The KL grade III group patients showed a 38.5 value before the procedure that rose to 52.1 at 6 months post-treatment and fell to 37.3 at 1 year post-treatment. The change in IKDC score was analyzed by repeated measured ANOVA analysis, and the clinical effects between KL grade I, II, and III groups had a decreased tendency ($P = 0.022$) (Fig. 5). Unlike the correlation between VAS score and KL grade system, differences between KL grades I and II, and grades II and III were statistically significant.

If PFJ degeneration occurred, the timing of relapse pain needed to be at 7.9 months on average; if not present, relapse pain needed to occur at an average of 10.2 months. The measured ANOVA test showed statistical significance ($P = 0.038$); however, there was no statistical significance between KL group and PFJ degeneration ($P > 0.05$).

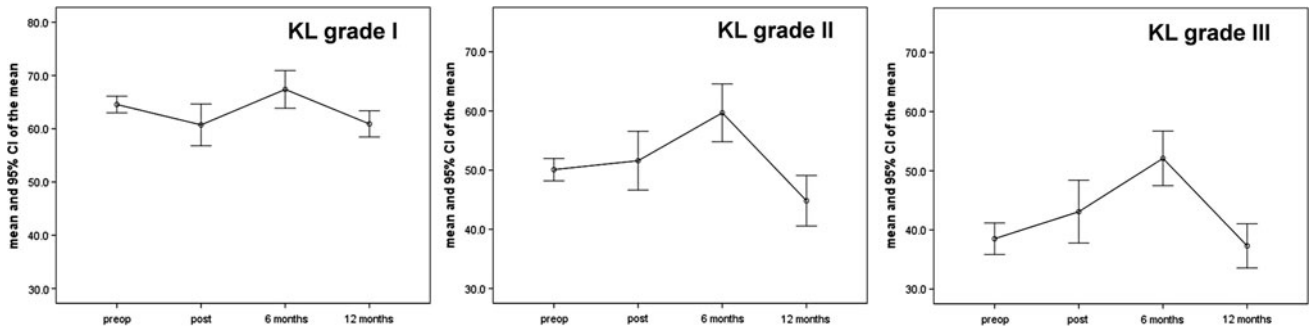

Fig. 5 Changes of IKDC score according to KL grade. Low KL grade showed a more effective and continuing effect than high KL grade ($P < 0.05$)

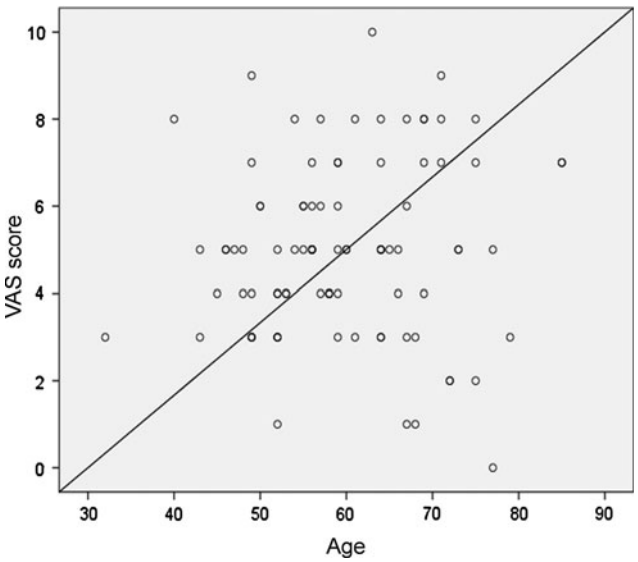

Fig. 6 Age and VAS score. Age and VAS score showed a positive correlation (slope = 0.1667)

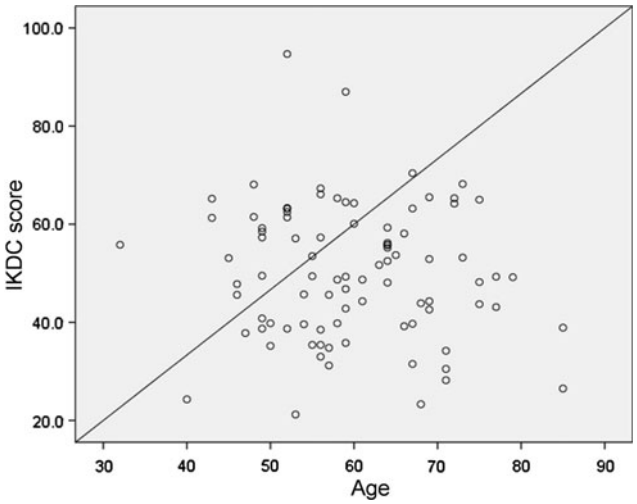

Fig. 7 Age and IKDC score. Age and IKDC score showed a positive correlation (slope = 1.3333)

The interrelationship between VAS score and patient age showed a slope of 0.1667 (Fig. 6). The IKDC score and patient age showed a slope of 1.3333 (Fig. 7), suggesting that as age increased, the clinical effect had a negative correlation in the linear regression analysis.

During our follow-up period, 41 patients (63.1%) complained of mild swelling or pain in 55 knees and that was resolved within 2 weeks. Mild local heating was observed in 10 knees (11.1%) by 7 patients (10.8%) and disappeared without any further treatment after 1 week. The administration of drugs including NSAIDs and steroids was avoided. No infections or other complications were reported.

Seven patients required surgical treatment after the follow-up period of this study. Five patients underwent arthroscopy with microfracture, one patient underwent total knee replacement arthroplasty, and one patient received uni-knee arthroplasty. All of these patients had symptomatic improvement after surgery.

Discussion

When arthroscopic evaluations were performed, it was found that articular cartilage lesions were present in approximately 60% of the patients [11]. Current treatment options for articular cartilage lesions progress linearly from palliative to reparative methods [12]. Non-operative solutions for OA and pain include administration of non-steroidal anti-inflammatory drugs (NSAIDs), glucosamine, chondroitin-sulfate, intra-articular injection of steroids, intra-articular injection of hyaluronic acid, and prolotherapy. Although these non-operative therapies only improve pain and the inflammatory state, they are widely used because the patient quality of life is much improved with these conservative therapies. Weight control and exercise therapy can show good results to decrease pain and improve joint function. When conservative treatments fail, operative treatments can be executed. Although operative options for OA include bone marrow stimulation (microfracture), chondrocyte implantation, osteochondral transplantation,

osteotomy, and arthroplasty, they are a limited treatment for degenerative OA because they have no ability to alter disease progression.

The pathophysiology of OA involves a combination of mechanical, cellular, and biochemical processes. These interactions lead to changes in the composition and mechanical properties of the articular cartilage [13]. Progression of OA is affected by an imbalance of pro-inflammatory and anti-inflammatory cytokines; this imbalance activates proteolytic enzymes and destroys cartilage [14]. Recent treatments for OA are concentrating on resolving these cytokine imbalances [15].

The PRP procedure has begun to receive attention as a regenerative treatment of cartilage and research focusing on the effects of PRP on cartilage lesions has gradually begun to surface. Growth factors regulate the expression of the chondrocyte phenotype that may play an important role in disease progression and PRP stimulates cell proliferation and the cartilage matrix. The hypothesis that PRP inhibits the catabolism of articular cartilage has recently emerged [16]. Transforming growth factor-beta (TGF-b) increases expression of the chondrocyte phenotype and stimulates the differentiation of mesenchymal stem cells and stromal deposits. In addition, TGF-b suppresses the synthesis of the cartilage glycoprotein mulin and inflammatory mediator IL-1 [17, 18]. Platelet-derived growth factor (PDGF) plays an important role in cartilage cell proliferation and maintenance of the cartilage phenotype by increasing the synthesis of glycoprotein [19]. Vascular endothelial growth factor (VEGF) plays a role to induce cartilage, and insulin-like growth factor (IGF) stimulates the synthesis of glycoprotein and degrades its catabolism [20]. Fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) are additional growth factors that function independently or in cooperation for the regeneration of articular cartilage metabolism [21]. Many growth factors are stored in platelet alpha bodies. PRP injections into the joint spaces will be considered a successful treatment when it results in efficient delivery, maintains high concentrations, and promotes healing [22].

In animal studies, PRP injection after anterior cruciate ligament reconstruction may prevent secondary OA and this progress was demonstrated experimentally [23]. Frisbie found that autologous conditioned serum (ACS) activates cartilage fibrillation and proliferates the synovial membrane to decrease bleeding in induced OA of controlled horse knees [6]. Gaissmaier revealed that platelet concentrates induce chondrocyte proliferation in articular cartilage in human experiments [24]. Mishra explained how to proliferate mesenchymal stem cells and differentiate chondrocytes [25]. Wei et al. [26, 27] introduced the possibility of a cell composite injection mixed with PRP and mesenchymal stem cells, and Anitua argued that intra-articular PRP injection facilitates the production of hyaluronic acid and induces neo-vascularization and cellular proliferation. Baltzer [7] reported that ACS injection is a better treatment than hyaluronic acid injection in the early treatment of OA.

Sanchez [28] suggested that in avulsion fractures of the articular cartilage in soccer players, PRP treatment could improve symptoms and accelerate healing. In degenerative OA, platelet concentrates had better patient results than hyaluronic acid injections in pain relief and functional improvement. Moreover, Kon evaluated 100 patients with OA treated with PRP injection, and the clinical improvement of joint function and pain relief were reported. In this study, mild pain and a temporary joint fluid collection after injection were reported but did not last for more than 2 days [8]. We observed similar complaints and complications and suppose that the cause of mild knee pain and heating were a mild inflammatory response due to the PRP injection, and expansion of the synovial joint space by the volume of PRP. Injection volume should be considered carefully.

cIn the 2-year follow-up of Kon, there was an increasingly deteriorating clinical course, with good results seen on average at 9 months estimated by statistical analysis. Overall, young people and those with low body mass index (BMI) had effective results for longer periods of time. In this study, as well as in Kon, relatively early degenerative arthritis showed better results, and in addition, we could make an accurate estimate of the duration of PRP injection [8]. Another study reported that the PRP injections showed significant improvement for 12 months after treatment [29]. It is meaningful that an accurate time of recurring knee pain was carried out in our study. The follow-up period in our study was limited but was long enough to determine the tendency of relapsing pain with decreased potential of the PRP effect and to evaluate the duration of PRP. We observed 20 people (30.8%) over 24 months. The clinical effect of PRP injections remained for 2 years, but continuously decreasing potential was noted. This means that PRP injection therapy has limited advantages when applied to advanced degenerative joint disease. The clinical effects of PRP intra-articular injection are expected to be worse in advanced degenerative joints and in old age. And their recent study reported that the autologous PRP intra-articular injections showed more and longer efficacy than hyaluronic acid injections in young patients [9].

OA is closely linked with PFJ degeneration and might be included in the same progress of this disease. When we are considering PRP injection for the treatment of OA, the results can be worse if the patient has PFJ degeneration. Therefore, we suggest that PFJ degeneration should be considered a meaningful factor when PRP intra-articular injection is planned.

A limitation of our study is that it was not a randomized trial with a formal control group, nor a comparative study

with a control group. However, we designed this study based on clinical experience and literature supporting the effects of PRP, and the comparative study was considered as unnecessary.

PRP injection therapy seems to be able to delay operative approaches in early degenerative disease. In cases of advanced degenerative joint disease, operative approaches such as arthroscopy, osteotomy, and arthroplasty can be better treatments. However, new biological joint treatments will be major therapies for OA in the near future.

Conclusion

Early osteoarthritis and young age are the appropriate conditions for treatment with PRP intra-articular injection and the presence of patellofemoral joint degeneration produces poor results. The duration of the effect of PRP is expected to remain for 8.8 months.

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