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Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions

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Abstract Platelet-rich plasma (PRP) is a natural concentrate of autologous blood growth factors experimented in different fields of medicine in order to test its potential to enhance tissue regeneration. The aim of our study is to explore this novel approach to treat degenerative lesions of articular cartilage of the knee. One hundred consecutive patients, affected by chronic degenerative condition of the knee, were treated with PRP intra-articular injections (115 knees treated). The procedure consisted of 150-ml of venous blood collected and twice centrifugated: 3 PRP units of 5 ml each were used for the injections. Patients were clinically prospectively evaluated before and at the end of the treatment, and at 6 and 12 months follow-up. IKDC, objective and subjective, and EQ VAS were used for clinical evaluation. Statistical analysis was performed to evaluate the significance of sex, age, grade of OA and BMI. A statistically significant improvement of all clinical scores was obtained from the basal evaluation to the end of the therapy and at 6–12 months follow-up ($P < 0.0005$). The results remained stable from the end of the therapy to 6 months follow up, whereas they became significantly worse at 12 months follow up ($P = 0.02$), even if still significantly higher respect to the basal level ($P < 0.0005$). The preliminary results indicate that the treatment with PRP injections is safe and has the potential to reduce pain and improve knee function and quality of live in younger patients with low degree of articular degeneration.

Keywords PRP · Cartilage · Knee · Intra-articular injection

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Introduction

The incidence of articular cartilage pathology has grown due to the marked increase in sports participation and greater emphasis on physical activity in all age groups [5]. Unfortunately, articular cartilage lesions, with their inherent limited healing potential [1, 3, 16, 26], are hard to treat and remain a challenging problem for orthopedic surgeons.

A variety of agents, such as nonsteroidal anti-inflammatory drugs, glucosamine, chondroitin-sulphate, hyaluronic acid, and glucocorticoids have been proposed as non-invasive solutions for pain treatment, improvement in function, and disability, and ultimately modification [10] of severe

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chondral degeneration and osteoarthritis with varying success rates. The initial pharmacologic management typically begins with analgesia and anti-inflammatory agents, through acetaminophen and NSAIDS [12]: the potential cardiovascular and gastrointestinal toxicity, the large apparent variation in the individual response to each drug and the absence of clear clinical data regarding the therapeutic potency could represent limits for a correct administration of symptoms [31]. Topical agents have only been proven useful for short-term use of mild-to moderate pain in osteoarthritis [14]. Intra-articular injections of corticosteroids, indicated by some studies, are of short-term benefit [22]. Moreover, some evidence suggests that they are not able to alter the natural history of the disease and may have deleterious consequences on knee structures [18]. Glucosamine, chondroitin-sulphate, and intra-articular hyaluronic acid have not been clearly demonstrated to be effective either, and due to the continuing controversies and lack of common accepted beneficial evidence should not be considered ideal procedures for the treatment of chronic severe chondropathies or osteoarthritis [4, 20].

Current research is investigating new methods of stimulating repair or replacing damaged cartilage, such as matrix metalloproteinase inhibitors, gene therapy, cytokine inhibitors, artificial cartilage substitutes, and growth factors [29]. In particular, the most recent knowledge regarding tissue biology highlights a complex regulation of growth factor for the normal tissue structure and the reaction to tissue damage. The influence of the growth factors in cartilage repair is now being widely investigated in vitro and in vivo [6, 9, 11, 25, 28]. Platelet-rich plasma (PRP) is a natural concentrate of autologous growth factors from the blood. The method is simple, low cost, and minimally invasive. Currently, a wide range of experiments is taking place in different fields of medicine in order to test the potential of enhancing tissue regeneration [2, 22].

The aim of our study is to explore this novel approach in treating degenerative lesions of articular cartilage. The objective of this pilot study is first to evaluate the safety of our protocol, by gathering and assessing the number, timing, severity, duration, and resolution of related adverse events. The second aim of the study is to analyze the short-term results obtained, to determine feasibility, indication criteria, and application modalities for further wider studies.

Our hypothesis is that the utilization of PRP could bring a stimulation of the chondral anabolism and a reduction of the catabolic processes. PRP may also influence the overall joint homeostasis, reducing synovial membrane hyperplasia.

Materials and methods

One hundred consecutive patients were enrolled and treated with PRP intra-articular knee injections. The following criteria for patient selection were used: history of chronic (at least 4 months) pain or swelling of the knee and imaging findings (radiograph or MRI) of degenerative changes in the joint. Exclusion criteria were systemic disorders, such as diabetes, rheumatoid arthritis, major axial deviation (varus $> 5°$, valgus $> 5°$), hematological diseases (coagulopathies), severe cardiovascular diseases, infections, immunodepression, patients in therapy with anticoagulants–antiaggregants, use of NSAIDs in the 5 days before blood donation, patients with Hb values of <11 and platelets values of $<150{,}000$/mmc. Ninety-one patients were prospectively evaluated at a 2, 6, and 12 months follow-up, 5 were lost at follow up, whereas 4 were excluded from the study because they did not complete the treatment: 3 patients stopped the treatment after the first injection for personal reasons and, in the other case, we decided to stop treatment because of a marked swelling and pain response after the injection. The patients analyzed were 57 men and 34 women, with a median age value of 47 years (range 24–82). Sixty-seven patients were affected by a monolateral lesion, whereas 24 patients presented a bilateral lesion, for a total of 115 knees treated. The mean BMI was 25 ± 3 (ranging from 18 to 32) and 27 patients had previously undergone knee surgery. All the patients presented a chronic degenerative condition; 58 knees presented a degenerative chondral lesion (Kellgren 0), 33 an early osteoarthritis (Kellgren I–III), while 24 knees had advanced osteoarthritis (Kellgren IV).

Platelet-rich plasma preparation

The procedure consisted of a 150-ml venous blood sample (collected in a bag containing 21 ml of sodium citrate) taken for every lesion treated. A complete peripheral blood count was also collected at the time of the initial blood draw. Then two centrifugations (the first at 1,800 rpm for 15 min to separate erythrocytes, and a second at 3,500 rpm for 10 min to concentrate platelets) produced a unit of 20 ml of PRP. All the procedures were performed in the same office setting. The unit of PRP was divided into 4 small units of 5 ml each. All the open procedures were performed in an A-class sterile hood. One unit was sent to the laboratory for analysis of platelet concentration and quality tested (platelet count and bacteriological test), one unit was used for the first injection within 2 h, and the other 2 units were stored at $-30°C$. The total number of platelets per millilitre in the PRP represented a mean increase of 600% compared with whole blood values, and an average of 6.8 million platelets were given to the lesion site at every injection. Injections were administered every 21 days; for the second and third treatments, the samples were thawed in a dry-thermostat at 37°C for 30 min just before application. Before the injection, 10% of

Ca-chloride (Ca^{2+} = 0.22 mEq × dose) was added to the PRP unit to activate platelets.

Treatment procedure and follow-up

The skin was sterilely dressed and the injection was performed through a classic lateral approach using a 22-g needle. At the end of the procedure, the patient was invited to bend and extend the knee a few times, to allow the PRP to distribute itself throughout the joint before becoming gel (Fig. 1). After the injection, the patients were sent home with instructions to limit the use of the leg for at least 24 h and to use cold therapy/ice on the affected area for pain. During this period, the use of non-steroidal medication was forbidden. During the treatment period, rest or mild activities (such as an exercise bike, mild exercises in pool) were indicated, and subsequently the gradual resumption of normal sport or recreational activities was allowed as tolerated. All complications and adverse events were recorded. Patients were prospectively clinically evaluated before the treatment, at the end of the treatment (2 months after the first injection) and at the 6 and 12 month follow-ups. All results are presented as the number of knees (not the number of individuals). IKDC, objective and subjective, and EQ VAS were used in clinical evaluation. The patient's satisfaction was also recorded.

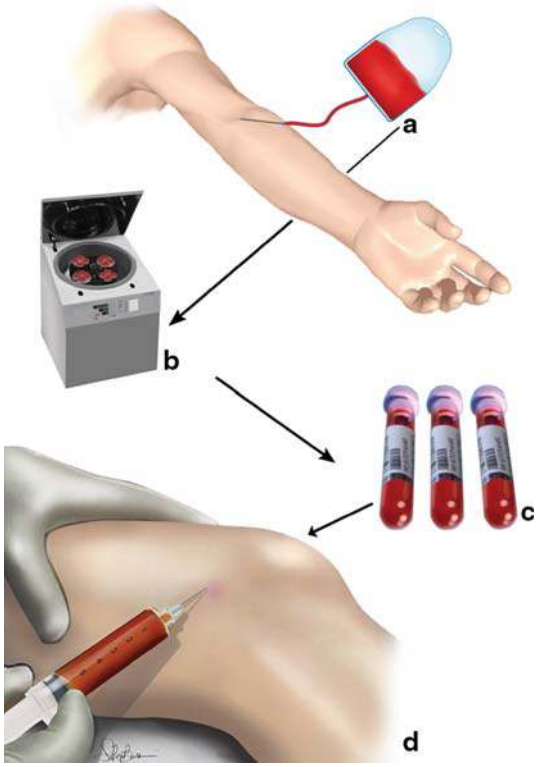

Fig. 1 The blood sample is processed, obtaining 5 ml PRP samples for the intra-articular injections

Statistical analysis

All statistical analyses were carried out using the SPSS (Statistical Package of Social Sciences, Chicago, IL, USA) for Windows software program version 13.0. A P value of less than 0.05 was considered statistically significant. The results were expressed as mean ± SD. The Wilcoxon test, the Mann–Whitney test, the Paired T test, the Kruskal–Wallis test and the One Way ANOVA test were used to test for significant differences between baseline band and various follow-up measurements. The Spearman's and the Pearson's statistical correlations were used to determine the parameters that statistically influenced the clinical outcome.

This clinical experimentation was approved by the Hospital Ethics Committee and the informed consent of all patients was obtained before the treatment.

Results

No major adverse events related to the injections were observed during the treatment and follow-up period. In only one case, a patient presented a marked pain response with swelling after the injection, which spontaneously resolved itself after 2 weeks. In some cases, slight pain was present during first 2 or 3 days. A statistically significant improvement of all clinical scores was obtained from the basal evaluation, to the end of the therapy and then at both the 6 and 12 month follow-ups. Eighty per cent (73/91) of patients were satisfied with their treatment results. The IKDC objective score passed from 46.1% of normal and nearly normal knees before the treatment (9A, 44B, 42C, and 20D) to 78.3% of normal and nearly normal knees (37A, 53B, 18C, and 7D) at the end of the therapy, then to 73.0% (36A, 48B, 20C, and 11D) and 66.9% (32A, 45B, 23C, and 15D) at 6 and 12 month follow-ups, respectively, showing a statistically significant improvement ($P < 0.0005$) at each of the follow-up times with respect to the basal level. The improvement was maintained from the end of the therapy to the 6 month follow-up, with an only slight tendency of worsening ($P = 0.08$), whereas a statistically significant decrease in the results was observed in the period between the 6 and 12 month follow-ups ($P = 0.018$). Similarly, the IKDC subjective score improved markedly from the basal evaluation to the end of therapy and the follow ups at 6 and 12 months ($P < 0.0005$), passing from 40.5 ± 10.4 before the treatment to 62.5 ± 15.9 at 2 months and 62.6 ± 18.6 and 60.6 ± 18.9 at the 6 and 12 month follow-ups, respectively. The results remained stable from the end of the therapy to the 6 month follow-up, whereas they became significantly worse at the 12 month follow-up ($P = 0.02$),

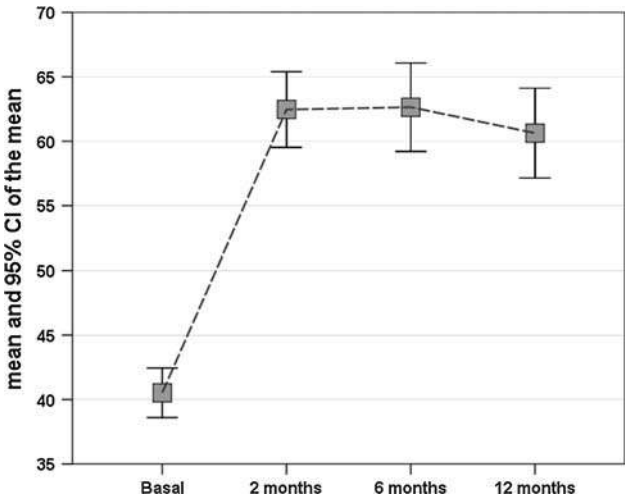

Fig. 2 Health status evaluated with IKDC Subjective score (0–100)

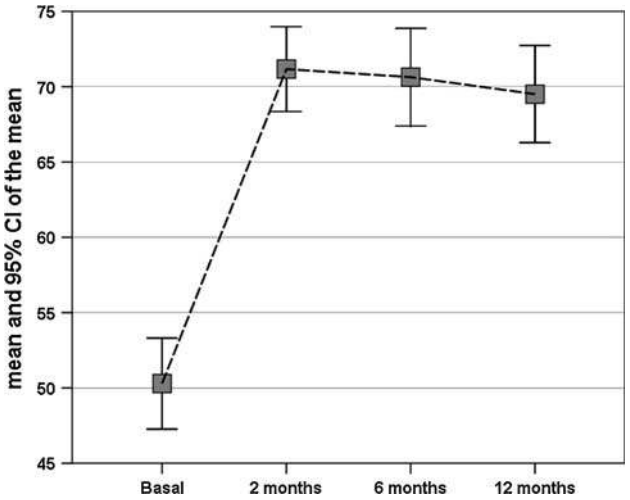

Fig. 3 Health status evaluated with EQ-VAS score (0–100)

even if still significantly higher with respect to the basal level ($P < 0.0005$) (Fig. 2). The same trend was confirmed by the EQ VAS evaluation, which improved from 50.3 ± 16.4 to 71.2 ± 15.2 at 2 months, 70.6 ± 17.5 at 6 months and 69.5 ± 17.4 at the final evaluation, with statistically significant higher scores at all the follow-up times with respect to the basal level ($P < 0.0005$), and a tendency (even if not statistically significant in this case: $P = 0.2$) of worsening over time (Fig. 3).

In order to establish the indications for this type of treatment, we tried to determine the parameters that influenced the clinical outcome. We found overall lower objective scores in older patients, before the treatment ($P = 0.043$) and at the different follow up times ($P = 0.005$ at 2 months, $P = 0.001$ at 6 months and $P = 0.013$ at 12 months), and most importantly, a scarce response to the treatment, with a lower improvement at the 6 months follow-up ($P = 0.049$) with respect to younger patients. A lower effect of the platelet concentrate in older patients was also confirmed analyzing the IKDC subjective evaluation (rho $= -0.331$, $P < 0.0005$) and EQ VAS scores (rho $= -0.389$, $P < 0.0005$) (Fig. 4). However, older patients also presented more severe changes of the joint ($P < 0.0005$), and the degree of articular degeneration was also significantly correlated to the clinical outcome (Table 1; Fig. 5). While analyzing older patients (>65 years) affected by advanced osteoarthritis separately, we found a significant improvement in the IKDC subjective evaluation in only 30% of the cases (3/10). Clinical results were not influenced by previous surgery. Finally, further analysis showed worse results were shown in women ($P < 0.0005$) in the subjective evaluation, and a significantly lower improvement at the 2 months follow-up in patients with higher BMI (rho $= -0.187$, $P = 0.045$), with a similar tendency at the 6 months follow-up (rho $= -0.1637$, $P = 0.08$).

Discussion

The most important finding of the present study was to investigate this novel biological approach for the treatment of knee degenerative pathology. In recent years, there has been an increasing prevalence of the use of autologous blood products that might provide cellular and humoral mediators to favor tissue healing in a variety of applications. The rationale is based on the activity of blood growth factors. The growth factors are a diverse group of polypeptides that have important roles in the regulation of growth and tissue development, determining the behavior of all cells, including chondrocytes. The understanding of their effects on chondrocytes is progressing rapidly and many growth factors have been identified as aiding in the regulation of articular cartilage. Most of the studies include the transforming growth factor-beta super-family (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) [17].

In particular, TGF-β is one of the most important factors involved in the process of cartilage regeneration; its functions include the increase of chondrocyte phenotype expression [19, 27], the chondrogenic differentiation of mesenchymal stem cells [15, 29], matrix deposition [6] and counteract with most of the suppressive effects of inflammatory mediators IL1 on cartilage-specific macromolecules synthesis [19]. PDGF also plays an important role in the maintenance of hyaline-like chondrogenic phenotype, increases chondrocyte proliferation, upregulates proteoglycan synthesis, and is a potent chemotactic factor for all cells of mesenchymal origin [25]. IGF is

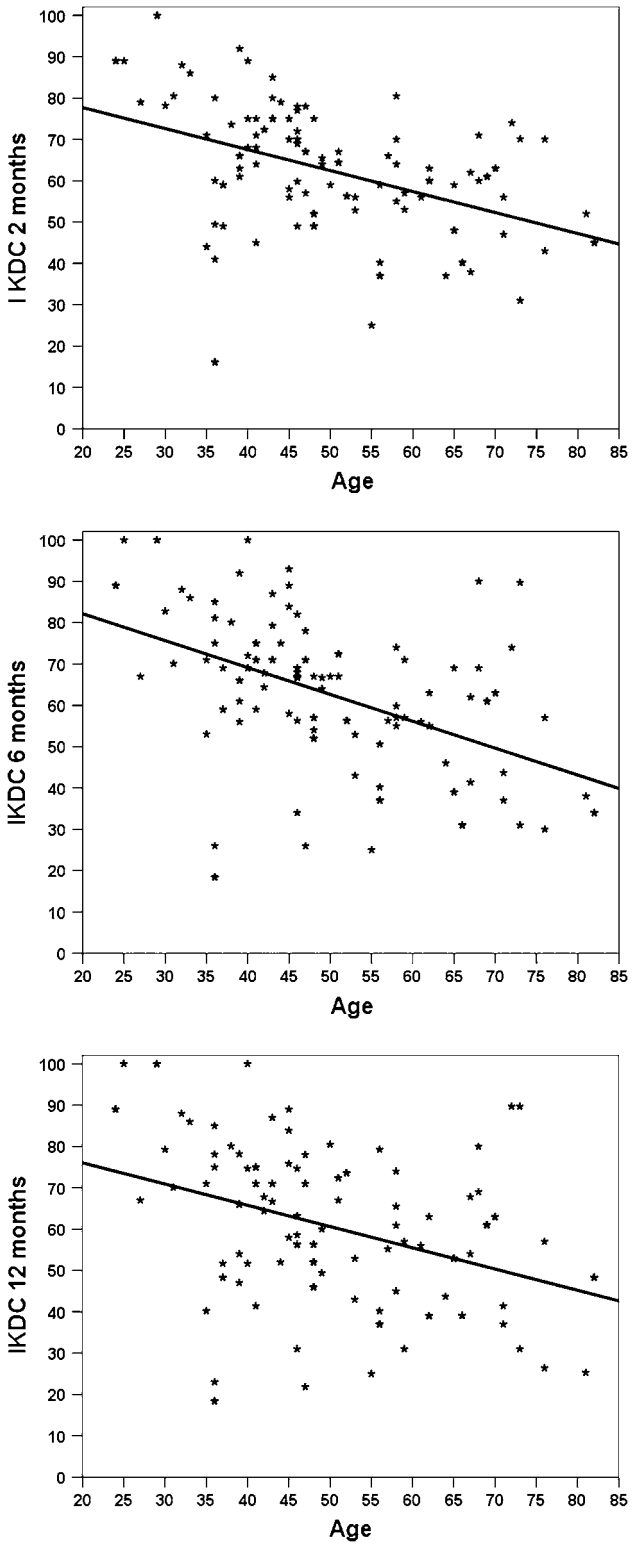

Fig. 4 Correlation between age and clinical outcome: older patients obtained worse IKDC subjective results at all the follow up times (2, 6, and 12 months) evaluated

another important cartilage anabolic factor [13] and it may have a role in augmenting the effects of other growth factors found in cartilage [17, 29]. Many other growth factors are involved in cartilage regeneration and metabolism, like FGF and HGF, and they may have chondroinductive actions, independently or even more so with additive effects and synergistic interaction [17]. PRP is a blood product that allows in a simple, low cost, and minimally invasive way to obtain a concentration of many of these growth factors [6, 9, 11, 25, 28]. Platelets contain storage pools of growth factors including PDGF, TGF β, IGF-1, FGF and many others. Cytokines, chemokines, and newly synthesised metabolites are also released [22]. PRP derived from centrifugation of autologous whole blood contain a platelet concentration four to five times higher than that of normal blood. The platelet concentrate is activated by the addition of calcium chloride, and this results in the formation of platelet gel and the release of a cascade of growth factors. The administration in the form of platelet gel provides an adhesive support that can confine secretion to a chosen site [2].

Blood derived growth factors have already been studied for their potential in helping cartilage repair and documented in the literature. Frisbie [7] administrated autologous conditioned serum (ACS) in horses with experimentally induced osteoarthritis, obtaining significant clinical improvement in lameness, decreased synovial membrane hyperplasia, less gross cartilage fibrillation, and synovial membrane hemorrhage and an increased synovial fluid concentration of interleukin-1 receptor antagonist. Gaissmaier [8] investigated the effect of human platelet supernatant (hPS) on chondrocyte proliferation and differentiation and concluded that addition of hPS may accelerate chondrocyte expansion, even though it can also lead to their dedifferentiation. Saito [21] documented preventive effects against OA progression with the administration of gelatin hydrogel microspheres containing PRP in a rabbit model. PRP has also been used as injectable scaffold for tissue engineering. Wu [30] investigated the feasibility of PRP to support chondrogenesis: the gelled PRP provided a 3-dimensional environment for seeded chondrocytes and was successfully used to deliver chondrocytes in cartilage defects in a rabbit model. Sánchez [24] described a case report where plasma rich in growth factors was used to treat an articular cartilage avulsion in a soccer player, obtaining an accelerated and complete articular cartilage healing. Finally, he reported [23] preliminary results about the effectiveness of intra-articular injections of an autologous preparation rich in growth factors for knee OA treatment in

Table 1 Correlation between the degree of joint degeneration and the clinical outcome at different follow-up times

	Degenerative chondropathy	Early osteoarthritis	Advanced osteoarthritis	*P* values
EQ VAS				
Basal	50.9 ± 15.6	51.8 ± 17.2	50.3 ± 16.4	NS
2 months	75.6 ± 12.6	71.6 ± 14.9	60.0 ± 16.4	0.001
6 months	78.0 ± 13.7	67.5 ± 18.9	57.1 ± 15.0	<0.0005
12 months	78.9 ± 13.3	69.2 ± 17.9	56.9 ± 15.9	<0.0005
IKDC S				
Basal	43.1 ± 9.2	40.0 ± 11.8	34.9 ± 8.9	0.004
2 months	70.1 ± 12.6	59.5 ± 13.8	48.1 ± 14.8	<0.0005
6 months	72.4 ± 13.6	58.9 ± 17.2	44.2 ± 15.0	<0.0005
12 months	68.7 ± 16.2	56.8 ± 17.8	46.4 ± 16.6	<0.0005

an observational retrospective cohort study on 30 patient, suggesting the safety and usefulness of this treatment approach.

These studies and others suggest an important role for these potent biological regulators of chondrocytes in cartilage repair. However, for the time being, the evidence base for PRP clinical use is still in its infancy, and there are only a few papers that specifically address treatment applications in the orthopedic field.

The primary objective of this pilot study was to evaluate the safety of our protocol, by gathering and assessing the number, timing, severity, duration, and resolution of related adverse events. No complications such as infection, marked muscle atrophy, deep vein thrombosis, fever, hematoma, tissue hypertrophy, adhesion formation, or other major adverse events occurred among 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, except in one case where marked pain and swelling were successfully treated in 2 weeks (in this case, we preferred to stop the treatment). The secondary aim of the study was to evaluate the preliminary results obtained, in order to determine the feasibility and potential of this new therapeutic approach, and to analyze indication criteria and application modalities for further studies. For this purpose, a group of 100 consecutive patients affected by degenerative pathology of articular knee cartilage was enrolled for the treatment with autologous PRP via multiple injections. We analyzed 91 patients (115 knees) who completed the treatment and were available for the 2, 6, and 12 months follow-up, and obtained a statistically significant improvement in all the parameters evaluated. The good results achieved at the end of the therapy were maintained at the 6 months follow-up, whereas a tendency of worsening was observed at 1-year evaluation. However, even if a significant improvement was demonstrated, the mean clinical outcome achieved allowed most of the patients only a normal daily activity life. In any case, due to the high average age, the low score at the end of the therapy was often explained by the low patient activity level, rather than from any persistent knee pain or functional limitation. Further analysis was performed in order to evaluate the influence of the different variables. Better results were achieved in younger patients, and a similar correlation was observed in the most degenerated joints. This could be expected and easily explained by the low percentage of living and vital cells and therefore the low response potential to the growth factors. In addition, extensive joint damage in severe osteoarthritis is hardly reversible. A correlation was also found with sex, with worse results in women. Results were also correlated with the patients BMI: at 2 months, worse results were found in patients with a higher BMI; the low number of overweight patients in our study, however, did not allow us to better analyze the influence of weight at the

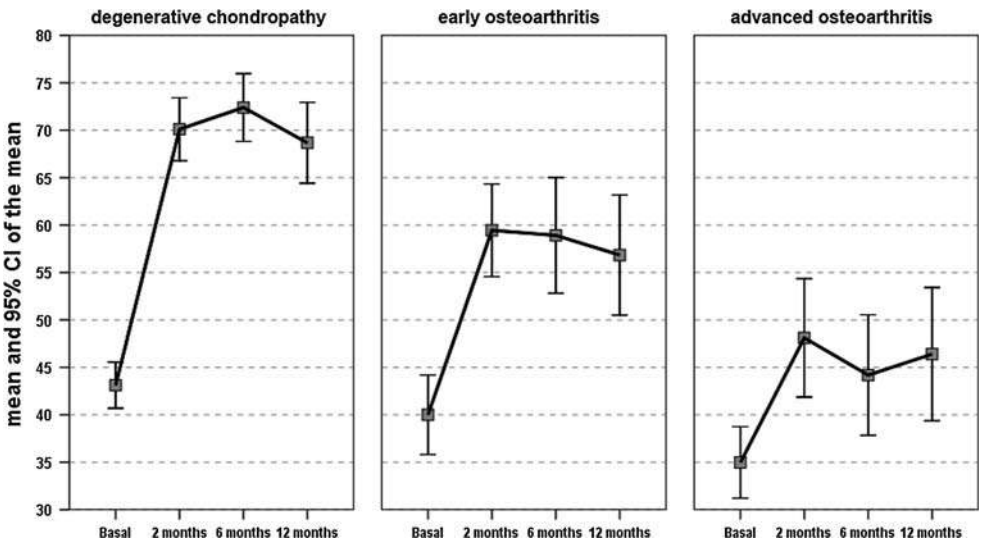

Fig. 5 Patients with degenerative chondropathy achieved better results with respect to patients affected by early osteoarthritis, who presented a higher improvement compared to patients with advanced osteoarthritis

different follow up times. Finally, other factors, such as previous surgery, did not influence the clinical outcome. Unexpectedly good results, however, were also obtained in three cases in older patients with severe osteoarthritis. We suppose that this could be explained by the fact that injected platelets may act at different levels and are not stimulating the chondral anabolism or slowing the catabolic processes. PRP may also influence the overall joint homeostasis, reducing synovial membrane hyperplasia and modulating the cytokine level, thus leading to an improvement in the clinical outcome, even if only temporarily and without affecting the cartilage tissue structure and joint degenerative progression [7]. Further studies are needed to confirm the results obtained and to understand the mechanism of the action, evaluating if there is only a temporary symptom improvement or if PRP may also play a more important role through disease modifying properties. The limitations of this study are the lack of a control group and the fact that the evaluation of the results only took place at a short term follow up. We analyzed our patients at a maximum follow up period of 12 months because, as for other injective therapies, the treatment can be repeated after a certain time interval. In any case, we believe that the main benefit of this type of therapy is expected in the short term. Promising results were obtained regarding safety, feasibility and the short-term effectiveness of this treatment option. This report documents our experience on autologous platelet-derived growth factor injections as a treatment of knee cartilage degeneration, which may represent a low-invasive and safe alternative in patients with chondropathy or early osteoarthritis. We suppose that PRP injections have a clinical relevance reducing inflammatory and degenerative articular processes and improving knee function and quality of life.

Conclusion

The preliminary short-term results of our pilot study are encouraging and indicate that treatment with autologous PRP intra-articular injections is safe, and may be useful for the treatment of early degenerative articular pathology of the knee, aiming to reduce pain and improve knee function and quality of life. However, randomized controlled studies will be needed to confirm the real potential and to evaluate the durability of this procedure, to better identify indication criteria and to improve application modalities. Further studies evaluating this new technique for treating cartilage degenerative pathology are in progress.

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