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Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis

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Abstract
Purpose Platelet-rich plasma (PRP) therapy is a simple, low-cost and minimally invasive method that provides a natural concentrate of autologous blood growth factors (GFs) that can be used to enhance tissue regeneration. In a previous analysis of a 12-month follow-up study, promising results were obtained when treating patients affected by knee degeneration with PRP intra-articular injections. The main purpose of this study was to investigate the persistence of the beneficial effects observed.
Methods Of the 91 patients evaluated in the previous 12-month follow-up study, 90 were available for the 2-year follow-up (24 patients presented a bilateral lesion, in a total of 114 knees treated). All of the patients presented a chronic knee degenerative condition and were treated with three intra-articular PRP injections. IKDC and EQ-VAS scores were used for clinical evaluation. Complications, adverse events and patient satisfaction were also recorded.
Results All of the evaluated parameters worsened at the 24-month follow-up: these parameters were at significantly lower levels with respect to the 12-month evaluation (the IKDC objective evaluation fell from 67 to 59% of normal and nearly normal knees; the IKDC subjective score fell from 60 to 51), even if they remained higher than the basal level. Further analysis showed better results in younger patients ($P = 0.0001$) and lower degrees of cartilage degeneration ($P < 0.0005$). The median duration of the clinical improvement was 9 months.
Conclusions These findings indicate that treatment with PRP injections can reduce pain and improve knee function and quality of life with short-term efficacy. Further studies are needed to confirm these results and understand the mechanism of action, and to find other application modalities, with different platelet and GF concentrations and injection timing, which provide better and more durable results.

Keywords PRP · Cartilage · Knee · Intra-articular injection

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Introduction

The number of knee cartilage lesions is growing due to increased emphasis on physical activity in all age groups,

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and patients' expectation with regards to recovery is also rising [31]. Unfortunately, the management of chondral disease is challenging because of its inherent low healing potential. In fact, the regeneration ability of cartilage is limited due to its isolation from systemic regulation and its lack of vessels and nerves [6, 7, 22]. Biomechanical, metabolic and biological changes may lead to the loss of tissue homoeostasis, resulting in an accelerated loss of the articular surface and followed by end-stage arthritis [13].

Numerous approaches have been proposed as non-invasive solutions for pain treatment, improving function and ultimately modifying the course of knee degenerative processes; however, they may offer only short-term benefits and present limits such as side effects or even deleterious consequences on knee structures [4, 12, 16, 18, 28, 33]. Finally, they have not been clearly shown to be able to alter the natural history of the disease, and yet, none of the currently available treatments can be considered an ideal procedure for the treatment of chronic severe chondropathy or osteoarthritis [8, 21].

Current research is aimed at investigating new methods of stimulating the repair of damaged cartilage. In particular, the most recent knowledge regarding tissue biology highlights the complex regulation of growth factors (GFs) for the normal tissue structure and the reaction to tissue damage, and the influence of these growth factors on cartilage repair has been widely investigated in vitro and in vivo [1, 14, 16, 27, 29]. Platelet-rich plasma (PRP) therapy is a simple, low-cost and minimally invasive method that allows a natural concentrate of autologous growth factors to be obtained from the blood. This therapy is widely experimented in different fields of medicine to test its potential to enhance tissue regeneration [9, 25]. In a previous study, 91 patients affected by a knee degenerative condition were treated with 3 PRP intra-articular injections and assessed at 12-month follow-up. The preliminary results indicated that this procedure was safe and reduced pain and improved knee function and quality of life in younger patients with a low degree of articular degeneration [15].

The primary aim of this study was to determine whether the promising results obtained at 12 months were maintained over time and establish whether there were significant differences between results achieved at 1 and 2 years of follow-up. A secondary aim of the study was to determine the patients' characteristics that may have influenced the results obtained.

Materials and methods

The study was approved by the Hospital Ethics Committee of the Rizzoli Orthopaedic Institute and informed consent of all patients was obtained.

The following diagnostic criteria for patient selection were used: history of chronic (at least 4 months) pain or swelling of the knee and imaging findings (X-ray or MRI) of degenerative changes of the joint. Exclusion criteria were systemic disorders such as diabetes, rheumatoid arthritis, major axial deviation (varus >5°, valgus >5°), haematological diseases (coagulopathy), severe cardiovascular diseases, infections, immunodepression, patients in therapy with anticoagulants or antiaggregants, the use of NSAIDs in the 5 days before blood donation and patients with Hb values of <11 and platelet values of <150,000/mmc.

Of the 91 patients evaluated in the previous 12-month follow-up study, 90 were available for the 24-month follow-up, whereas 1 patient was lost at the time of the follow-up study. These patients included 57 men and 33 women, with a mean age of 50 ± 14 years (range 24–82). Sixty-six patients were affected by a monolateral lesion and 24 patients presented a bilateral lesion, making a total of 114 knees treated. The mean BMI was 25 ± 3 (range 18–32), and 27 patients had undergone previous knee surgery: 13 meniscectomies, 8 LCA, 10 cartilage treatments (four microfractures, three-second generation autologous chondrocytes implantations, three shavings), and one osteotomy. All of the patients presented a chronic degenerative condition; 58 knees presented a degenerative chondral lesion (Kellgren 0), 32 knees presented early osteoarthritis (OA) (Kellgren I-III) and 24 knees were affected by advanced osteoarthritis (Kellgren IV) (Table 1).

Platelet-rich plasma preparation

The procedure entailed a 150-ml venous blood sample (collected in a bag containing 21 ml sodium citrate) for each knee treated. A complete peripheral blood count was also collected at the time of the initial blood donation. The samples were centrifuged twice (the first at 1,800 rpm for 15 min to separate erythrocytes, and the second at 3,500 rpm for 10 min to concentrate platelets) to produce a unit of 20 ml of PRP. All of the procedures were performed in the same laboratory setting. The PRP was then divided into four small units of 5 ml each. All of the open procedures were performed in an A-class sterile hood. Of the four smaller PRP units, one unit was sent to the laboratory for quality analysis (platelet count and bacteriological test), one unit was used for the first injection within 2 h and the other two 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 billion platelets were administered to the lesion site for each 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.

Table 1 Age, sex and BMI characteristics of the three pathology groups analysed

	Degenerative chondropathy	Early osteoarthritis	Advanced osteoarthritis	*P* values
Age	41.6 ± 7.9	54.5 ± 11.6	63.6 ± 13.1	$P < 0.0005$
	24–65	31–73	36–82	
Sex	M 42	M 18	M 13	n.s.
	F 16	F 14	F 11	
BMI	23.9 ± 2.8	25.9 ± 3.2	26.4 ± 3.9	$P < 0.0005$
	18–33	18–32	20–35	

Before the injection, 10% calcium chloride (Ca++ = 0.22 mEq × dose) was added to the PRP unit to activate the platelets [15].

Treatment procedure and follow-up

The skin was sterilely dressed, and the infiltration was performed using a classic lateral approach with a 22-g needle. At the end of the procedure, the patient was asked to bend and extend the knee a few times to allow the PRP to spread throughout the joint before becoming a gel.

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 to relieve pain. During this period, the use of non-steroidal medication was forbidden. During the treatment period, rest or mild activities (such as using an exercise bike or mild exercise in a pool) were permitted, and subsequently a gradual resumption of normal sport or recreational activities was allowed, as tolerated.

Patients were prospectively evaluated before and at the end of the treatment (2 months after the first injection), and at follow-ups 6, 12 and 24 months after the treatment. All results are presented as the number of knees (not the number of individuals). IKDC, objective and subjective, and EQ-VAS were used for clinical evaluation. Complications, adverse events and patient satisfaction were also recorded (we asked if patients they were satisfied with the treatment and that, considering their overall experience, they would repeat it if needed). For patients who decided to repeat the treatment between the 12- and 24-month follow-up because the beneficial effect had ended, or for those who were treated surgically because of knee degeneration, the final available follow-up before the new treatment was used for the 24-month follow-up evaluation.

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.

One-Way ANOVA was performed to test differences among means of different groups. When Levene's test for homogeneity of variance was significant or when the data were not normally distributed with the Kolmogorov–Smirnov test, the Mann–Whitney (two groups) or the Kruskal–Wallis (three groups or more) tests were used instead of ANOVA. The Sceffé test or non-parametric Least Significant Difference test were used as a post hoc pairwise analysis when the groups were more than two. The repeated measures ANOVA with the pairwise post hoc analysis via 95% CI at the Bonferroni correction was used to test differences among the different follow-ups of EQ-VAS and IKDC subjective follow-ups. The Friedman test with the pairwise post hoc analysis via the Wilcoxon test with the Bonferroni correction was used to test the difference of IKDC objective follow-ups.

Pearson's correlation (normally distributed data) or Spearman's rank correlation (not normally distributed data) was used to evaluate the influence of the continuous parameters on the outcome. The General Linear Model was used as multivariate analysis to asses the influence of patient characteristics over months of benefit.

Results

As previously reported, only one patient presented a marked pain response with swelling after the injection for 2 weeks. No other complications related to the infiltrations or severe adverse events were observed during the treatment and 24-month follow-up period.

The IKDC objective score increased from 47% of normal and nearly normal knees before the treatment to 78% at the end, then to 73 and 67% at the 6- and 12-month follow-ups, respectively, showing a statistically significant improvement ($P < 0.0005$) at all these follow-up times with respect to the basal level. The evaluation after 24 months showed a drop ($P = 0.04$) in the score to 59% in normal and nearly normal knees, even though mean results were still significantly better compared to the basal evaluation ($P = 0.0014$) (Table 2). Similarly, the IKDC subjective score improved markedly from the basal evaluation to the end of therapy and the follow-up study at 6

Table 2 IKDC objective evaluation

	A	B	C	D
Basal	9	44	42	19
2 m	37	52	18	7
6 m	35	48	20	11
12 m	31	45	23	15
24 m	22	45	29	18

and 12 months ($P < 0.0005$). The tendency of the score to fall at the 12-month follow-up (n.s.) was further amplified ($P < 0.0005$) in the 24-month evaluation (60 ± 19 points at 12 months and 51 ± 20 points at 24 months of follow-up), even though the results remained significantly higher than the basal level ($P < 0.0005$) (Fig. 1). The same trend was confirmed by the EQ-VAS evaluation, which improved markedly from the basal evaluation to the end of therapy and at the follow-up evaluations at 6 and 12 months ($P < 0.0005$), and presented a marked worsening over time, with a significantly lower score at the 24-month follow-up ($P < 0.0005$), even though it remained better than the basal level ($P < 0.0005$) (Fig. 2). The good level of satisfaction with the treatment results obtained at the 12-month follow-up was confirmed at the 24-month evaluation, with 80% (73/91) and 80% (72/90) of the patients being satisfied, respectively. Among these, 46% (33/72) of the satisfied patients asked for another injection when the beneficial effects had ended and were re-treated during the year between the 12- and 24-month follow-ups.

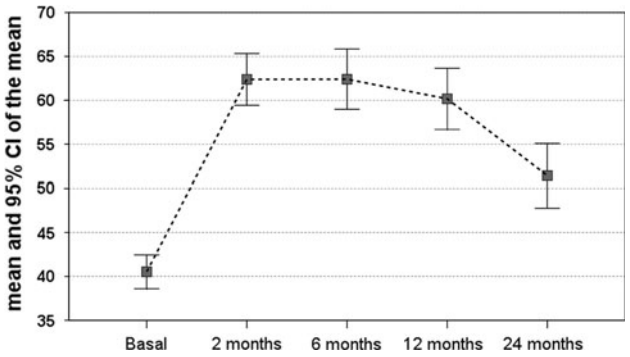

Fig. 1 Health status evaluated with IKDC Subjective score (0–100)

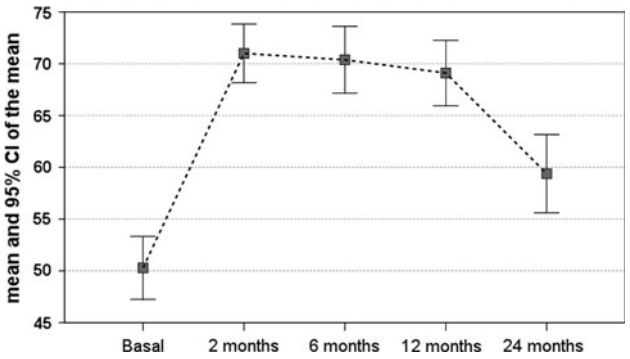

Fig. 2 Health status evaluated with EQ-VAS score (0–100)

The evaluation after 24 months showed a significant worsening of the results in all of the evaluated subgroups (degenerative chondropathy $P < 0.0005$, early OA $P < 0.0005$, advanced OA $P = 0.02$); however, better results were observed in cases with a lower degree of articular cartilage degeneration ($P < 0.0005$, Fig. 3) and in younger patients ($r = -0.421$, $P = 0.0001$, Fig. 4). The worst results were obtained from women in the subjective evaluation (44 ± 20 vs. 56 ± 18; $P = 0.0002$). Clinical results were not influenced by previous surgery.

Finally, we determined the length of action of the platelet concentrate injections: the mean duration of the beneficial effects was 11 ± 8 months. However, considering that some patients did not show any improvement and that other patients still had good results without worsening over time at the 24-month follow-up evaluation, we believe that the duration of the treatment is better shown by the median: 9 months (Fig. 5). The duration of the therapeutic effect was correlated with age, sex and degree of cartilage degeneration. Longer-lasting results were seen in younger patients ($r = -0.343$, $P < 0.0005$), men ($P = 0.002$) and in lower degrees of chondral degeneration ($P < 0.0005$) (Table 3). Multivariate analysis via GLM with sex and diagnosis as a fixed effect and age and BMI as covariates showed the months of benefit was influenced by sex ($\eta^2 = 0.042$, $P = 0.03$), diagnosis ($\eta^2 = 0.057$, $P = 0.04$), BMI ($\eta^2 = 0.058$, $P = 0.01$) and only a tendency for age (n.s).

Discussion

The most important finding of the present study is the duration of the PRP effect in the treatment of knee degeneration, when administered by three intra-articular injections to promote the healing potential of chondral tissue.

Chondrocytes are affected by numerous extracellular stimuli influencing the regulation of biosynthetic and catabolic activity, including mechanical stress and soluble factors [5]. An imbalance of regulatory factors, which may result from ageing, disease, or injury, may hinder tissue maintenance and repair, ultimately resulting in deleterious changes in gene expression, altered extracellular matrix, tissue degeneration and consequently an accelerated erosion of the articular surface, leading to end-stage arthritis [30]. Therefore, laboratory tests into therapeutic intervention are focused on the possibility of preserving normal homoeostasis or blocking or reversing structural damage,

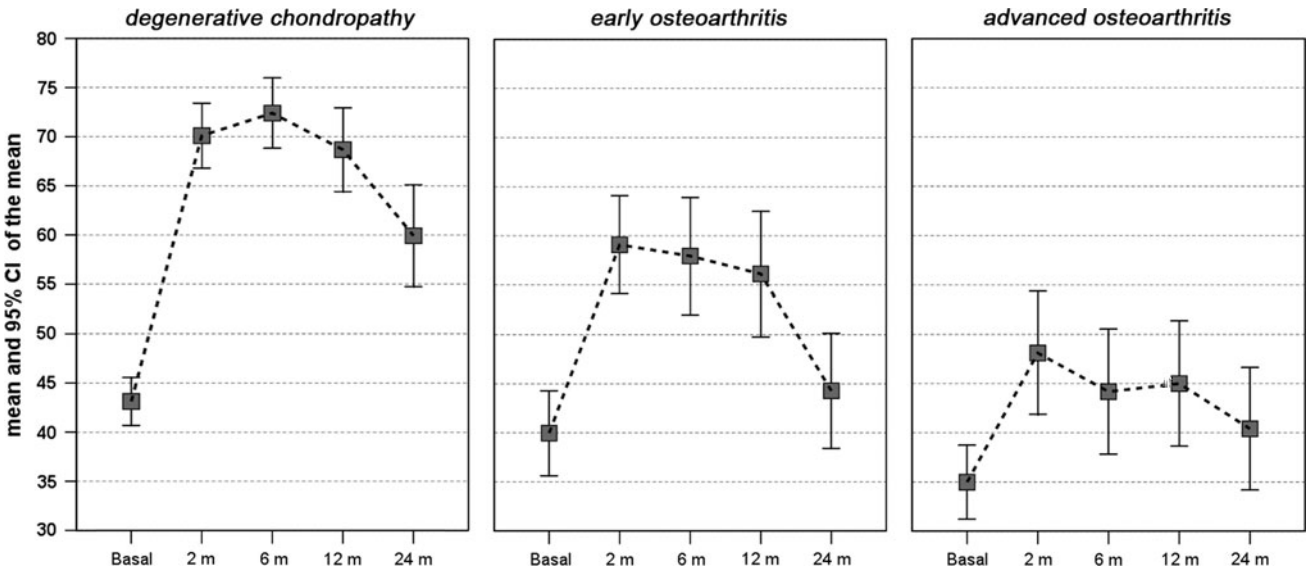

Fig. 3 Patients with degenerative chondropathy achieved a higher IKDC subjective score with respect to patients affected by early osteoarthritis, who presented a greater improvement compared to patients with advanced osteoarthritis. All subgroups presented a marked reduction in IKDC subjective score from the 12- to the 24-month follow-up

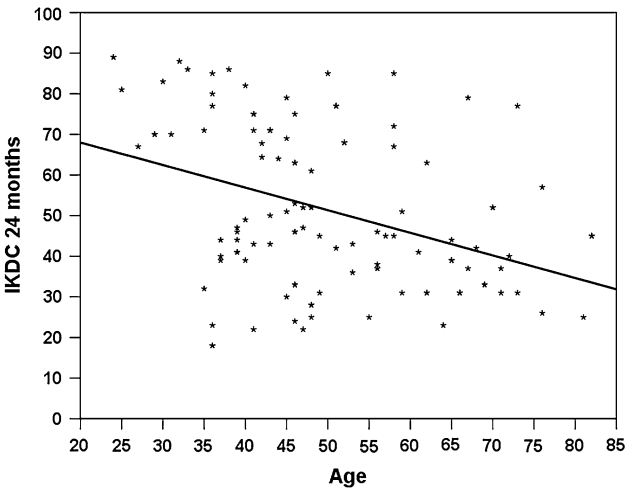

Fig. 4 Correlation between age and clinical outcome: older patients obtained the lowest IKDC subjective scores at the 24-month follow-up

to avoid or at least delay the need for more invasive surgical procedures. Several studies have described a complex regulation of growth factors involved in normal tissue structure and the reaction to tissue damage, and these studies show the importance and effectiveness of applying growth factors in healing damaged tissue [2, 9–11, 14, 17, 19, 20, 27, 29].

Blood-derived growth factors have already been studied for their potential to help cartilage repair and have been documented in the literature in both preclinical and clinical studies [23, 32]. In particular, Baltzer et al. [3] analysed the effect of autologous conditioned serum (ACS) in the treatment of patients with knee osteoarthritis. In their prospective, randomised, patient- and observer-blinded, placebo-controlled trial, they demonstrated that ACS injections considerably improved the clinical signs and symptoms of OA with results that are even superior to those of HA.

Recently, there has been increasing interest in the use of another autologous blood product, PRP, which might provide cellular and humoral mediators to promote tissue healing in a variety of applications. The rationale is based on the activity of blood growth factors carried in platelets, many of which have been shown to take part in the regulation of articular cartilage [1, 14, 16, 27, 29]. Platelets contain storage pools of growth factors in their α-granules [9], including PDGF, TGF β, IGF-1, FGF and many others, as well as cytokines and chemokines [25]. PRP is derived from the centrifugation of autologous whole blood and contains a platelet concentration that is 4 to 5 times higher than that of normal blood, thus offering a high concentration of GFs in physiological proportions. Some research suggests a possible role for PRP in the treatment of cartilage lesions [23, 26, 32]. In an observational retrospective cohort study using hyaluronan injections as a control, Sanchez et al. [24] showed interesting preliminary results using intra-articular injections of an autologous preparation rich in growth factors (PRGF) for the treatment of knee OA.

These studies suggest that these potent biological regulators of chondrocytes have an important role in cartilage repair. However, for the time being, the evidence for the clinical use of PRP is still in its infancy, especially regarding

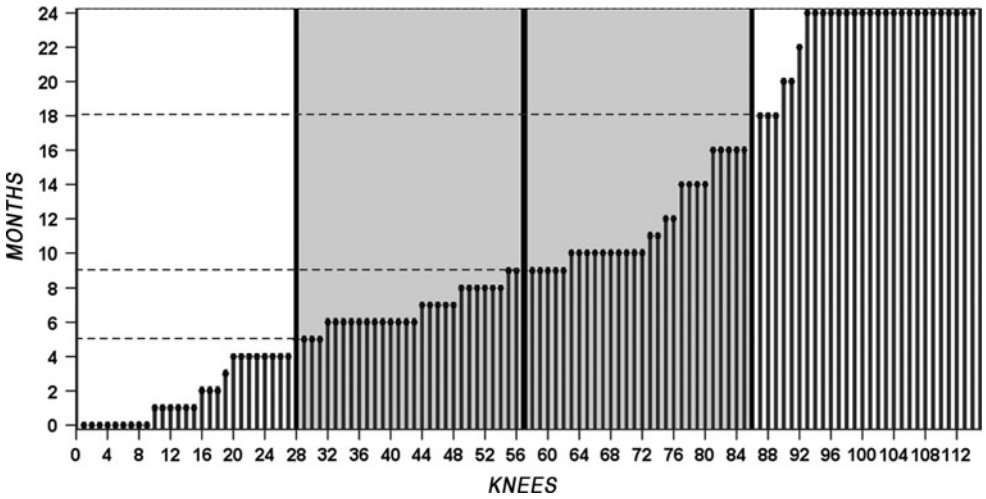

Fig. 5 Duration of the beneficial effect of PRP shown by the IKDC subjective score in the 114 knees treated and evaluated for 24 months after the injection cycle. The *grey* area represents the interquartile range of the results. The median duration of the beneficial effect is 9 months (25–75th percentiles: 5–18 months)

Table 3 Duration of the therapeutic effect

Patients	Months (mean ± SD)
All	10.9 ± 8.1
Men	12.6 ± 7.9
Women	7.8 ± 7.6
Deg chond	13.7 ± 7.7
Early OA	9.2 ± 6.9
Advanced OA	6.1 ± 7.8

the treatment of degenerative knee conditions via multiple PRP injections. A study was performed to explore this novel approach for the treatment of articular cartilage degenerative lesions. The preliminary results indicated that this procedure was safe and had the potential to relieve pain and improve knee function and quality of life in younger patients with a low degree of articular cartilage degeneration. Ninety-one patients (115 knees) were analysed at 12 months follow-up, and a statistically significant improvement in all of the parameters evaluated was observed.

The main purpose of this study was to investigate the persistence of the beneficial effects observed at a 24-month follow-up evaluation. An overall reduction was observed in all of the evaluated parameters, which were significantly lower at the 24-month follow-up when compared to the 12-month evaluation, despite remaining above the baseline values. Further analysis, performed to determine the indication criteria, confirmed the preliminary findings of the 12-month follow-up. In fact, despite the overall reduction in all of the subgroups, younger patients and those with a lower degree of cartilage degeneration still presented better results at the last follow-up. As in the previous study, the final evaluation confirmed that female patients showed the worst results, which was probably due to gender-specific biological and biomechanical characteristics, which might influence the etiopathogenesis, the effects of the GFs and ultimately, the clinical response to treatment. Other factors, such as previous surgery, did not influence the clinical outcome, and an improvement in pain and knee function could also be observed in patients who had undergone previous surgery. Finally, the median duration of clinical improvement was 9 months. It should be emphasized that we observed a wide range of PRP effect duration, which was found to be correlated with factors like age, BMI, sex and degree of cartilage degeneration. In fact, young men with degenerative chondropathy had not only more clinical benefit but also longer-lasting results.

The initial hypothesis was that the use of PRP might stimulate chondral anabolism and produce a reduction in the catabolic processes, thus leading to chondroprotective and chondroregenerative actions and therefore a symptomatic improvement. However, the clinical nature of this study makes it difficult to assess the disease-modifying properties of this approach. Moreover, despite the initial considerable improvement in clinical signs and symptoms of knee cartilage degeneration, the marked worsening observed at the 24-month follow-up indicates that the improvement due to PRP injections is mostly symptomatic, at least with this procedure. PRP probably influences the overall joint homoeostasis also through the reduction of synovial membrane hyperplasia and modulation of the cytokine level, thus leading to the observed improvement in the clinical outcome, albeit only temporarily and maybe without affecting the cartilage tissue structure or the progression of joint degeneration [10, 23]. Further studies will determine whether other application modalities, with different platelets/GF concentrations and injection times, may allow better and more durable results to be achieved.

The weak points of this study are the lack of a control group and the evaluation of the results only through clinical scores. The analysis of imaging or biological changes would allow a better understanding of the effect and mechanism of action of PRP.

However, this report shows the outcome of autologous platelet-rich plasma injections as a treatment for articular cartilage degeneration in humans, which produces a significant improvement in the clinical outcome of most patients especially in the short term. The treatment is most effective in younger male patients, with lower BMI and lower degrees of chondral degeneration. The interesting results obtained regarding the safety, feasibility and short-term efficacy of this treatment suggest that it may represent a minimally invasive and safe procedure that may be cyclically repeated in order to improve knee function and quality of life.

Further studies are needed to support these results and understand the mechanism of action of PRP. It still remains to be determined whether there is only a temporary improvement in symptoms or whether PRP therapy may play a more important role through disease-modifying properties, and whether different platelet concentrations or application modalities could further increase the clinical benefits offered by this new biological minimally invasive approach.

Conclusion

The clinical results of this pilot study at 24 months follow-up showed an overall reduction in all of the scores with respect to the promising results previously observed at the 12-months follow-up, despite being higher than the basal levels. These findings indicate that treatment with PRP injections has the potential to reduce pain and improve both knee function and quality of life with short-term efficacy, especially in younger patients with chondral degenerative lesions or early osteoarthritis. Despite the limited duration of its effect, the interesting clinical results observed suggest that this minimally invasive procedure may be cyclically applied in patients affected by knee degeneration to avoid or at least delay the need for more invasive surgical procedures.

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