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Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation

A Randomized Controlled Trial

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Background: Osteoarthritis (OA) is a common disease that will affect almost half the population at some point in their lives through pain and decreased functional capacity. New nonoperative options are being proposed to treat earlier stages of joint degeneration to provide symptomatic relief and delay surgical intervention.

Purpose: To evaluate the benefit provided by platelet-rich plasma (PRP) injections to treat knee joint degeneration in comparison with hyaluronic acid (HA), the most common injective treatment currently adopted for this condition.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 443 patients were screened, and 192 of them were enrolled in the study according to the following inclusion criteria: (1) unilateral symptomatic knee with history of chronic pain (at least 4 months) or swelling and (2) imaging findings of degenerative changes (Kellgren-Lawrence score of 0-3 at radiographs or MRI evidence of degenerative chondropathy). Patients underwent 3 weekly intra-articular injections of either PRP or HA. Patients were prospectively evaluated at baseline and then at 2, 6, and 12 months of follow-up using the International Knee Documentation Committee (IKDC) subjective score (main outcome), Knee injury and Osteoarthritis Outcome Score, EuroQol visual analog scale, and Tegner score. Range of motion, transpatellar circumference, patient satisfaction, and adverse events were also recorded.

Results: Two patients reported severe pain and swelling after HA injections, while no major adverse events were noted in the PRP group. However, PRP presented overall significantly more postinjection swelling and pain. Both treatments proved to be effective in improving knee functional status and reducing symptoms: the IKDC score in the PRP group rose from 52.4 ± 14.1 to 66.2 ± 16.7 at 12 months ($P < .0005$), and in the HA group it rose from 49.6 ± 13.0 to 64.2 ± 18.0 at 12 months ($P < .0005$). A similar trend was observed for all the clinical scores used. The comparative analysis of the 2 treatments showed no significant intergroup difference at any follow-up evaluation in any of the clinical scores adopted.

Conclusion: PRP does not provide a superior clinical improvement with respect to HA, and therefore it should not be preferred to viscosupplementation as injective treatment of patients affected by knee cartilage degeneration and OA.

Keywords: PRP; viscosupplementation; growth factors; intra-articular; injections; cartilage; osteoarthritis

Osteoarthritis (OA) is a common condition that will affect almost half the population at some point in their lives through pain and decreased functional capacity.[17,18,22] Although late stages of this condition are commonly treated by procedures such as metal resurfacing, new options are currently being proposed to treat earlier stages of joint degeneration.[16,20,23,25] Among these, a novel biological treatment approach, platelet-rich plasma (PRP), has been introduced into clinical practice as a minimally invasive solution to improve the status of the joint surface and allow a fast return to full activity.

PRP is a blood derivative that aims at concentrating platelets to take advantage of their properties.[33,36] In fact, once activated, platelets release a group of biologically active proteins that bind to the transmembrane receptors of their target cells, thus leading to the expression of gene sequences that ultimately promote cellular recruitment, growth, and morphogenesis and modulate inflammation as well.[1,35] Several in vitro studies, as well as preclinical studies using an animal model, provided the rationale for the clinical application of platelet concentrates, documenting positive effects and showing how intra-articular injections do not target only cartilage: PRP might also influence other tissues such as menisci and

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synovia and in the end affects the entire joint environment, which may lead to the improvement reported in clinical practice.[14]

However, despite the widespread application of PRP, there is no solid evidence in the literature to back up its real usefulness for the management of chondropathy and OA. Thus, the aim of this study was to evaluate the benefit provided by PRP to treat early stages of joint degeneration in comparison with another injective treatment: hyaluronic acid (HA). The hypothesis was that PRP would provide superior clinical results with respect to viscosupplementation for up to 12 months.

METHODS

Patients

The present randomized double-blind trial was approved by the hospital ethics committee and scientific board, and written consent was collected for each patient. This single-center trial was announced with advertisements on several web sites and journals. Patients contacted the researcher by telephone or email and received detailed information: the first eligibility screening was performed at this time. If patients seemed to be suitable for inclusion in the study, an appointment was made at the outpatient department, where an experienced orthopaedic physician evaluated suitability for inclusion according to the following criteria: (1) unilateral symptomatic knee with history of chronic pain (at least 4 months) or swelling and (2) imaging findings of cartilage degeneration, that is, chondropathy (Kellgren-Lawrence score of 0, detected by magnetic resonance imaging [MRI]) or osteoarthritis (Kellgren-Lawrence score of 1-3). The exclusion criteria were age greater than 80 years, Kellgren-Lawrence score more than 3, major axial deviation (varus $>5°$, valgus $>5°$), focal chondral or osteochondral lesion, presence of any concomitant knee lesion causing pain or swelling (ie, ligamentous or meniscal injury), inflammatory arthropathy, hematological diseases, severe cardiovascular diseases, infections, immunodepression, therapy with anticoagulants or antiaggregants, use of nonsteroidal anti-inflammatory drugs in the 5 days before blood donation, and hemoglobin count lower than 11 g/dL and platelet count lower than 150,000/mm^3.

Study Design, Randomization, and Intervention

This randomized controlled, double-blinded trial lasted 4 years (2009-2013) and was performed at the outpatient department of a highly specialized referral center for orthopaedics. Patients were randomly divided into 2 different treatment groups: those receiving 3 weekly intra-articular injections of PRP versus those receiving 3 weekly administrations of high-molecular-weight HA (Hyalubrix 30 mg/2 mL, molecular weight >1500 kDa; Fidia SpA). To keep the patients blinded, all of them underwent blood harvesting to obtain autologous PRP, which was used only in half of them. The randomization list (block randomization with block sizes of 8 patients) was provided by an independent statistician and kept in a dedicated office. In particular, progressively numbered, sealed envelopes containing the treatment allocation (PRP or HA) were used. The physician administering the treatment contacted the office just before performing the injection to know the patient allocation; the envelope was then opened to determine the treatment group and the patients included in the randomization list. Before the injection, the syringe was appropriately covered to prevent patients from discovering the substance they were receiving. After the injection, they were sent home with instructions to restrict the use of the leg for at least 24 hours and to use ice or other cold therapy on the affected area to relieve pain. The treatment consisted of 3 injections at 1-week intervals. During the treatment period, rest or mild activities were permitted, and subsequently a gradual resumption of normal sport or recreational activities was allowed as tolerated. The study was registered at clinicaltrials.gov (NCT01670578).

PRP Preparation Method

A single 150-mL unit of peripheral venous blood was harvested from each patient at our Hospital Transfusion Medicine Service. Then, 2 centrifugations were performed: the first at 1480 rpm for 6 minutes to separate erythrocytes and the second at 3400 rpm for 15 minutes to concentrate platelets, which provided 20 mL of PRP divided into 4 small units of 5 mL. One unit was sent to the laboratory for quality tests, and 3 units were stored at $-30°$C to be used later for the treatment after being thawed in a dry-thermostat at 37°C for 30 minutes. Before the injection, the PRP was activated by adding 10% calcium chloride. The preparation method used allowed the number of platelets per milliliter to increase by a mean of 4.6 ± 1.4 times with respect to baseline blood values. Leukocytes were also present, with a mean concentration of 1.1 ± 0.5 times with respect to the normal blood value.

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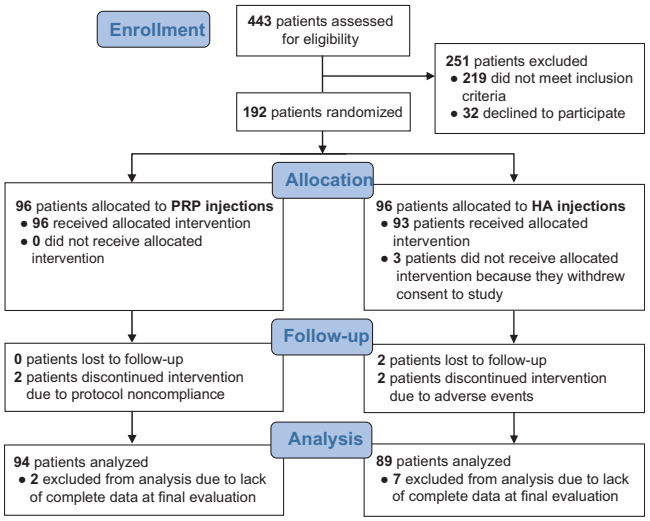

Figure 1. CONSORT flow diagram of the present randomized controlled trial. HA, hyaluronic acid; PRP, platelet-rich plasma.

Evaluation Tools and Follow-up

Patients were prospectively evaluated at baseline and then at 2, 6, and 12 months after the last injection; evaluation included the International Knee Documentation Committee (IKDC) subjective measure, Knee injury and Osteoarthritis Outcome Score (KOOS), EuroQol visual analog scale (EQ-VAS), and Tegner score. Range of motion and the transpatellar circumference of both the index knee and the contralateral knee were measured. Patient satisfaction and adverse events were also recorded. To guarantee the double-blinding of the trial, all the clinical evaluations were performed by an independent physician not involved in the injection procedure.

Statistical Analysis

Sample Size Calculation. A power analysis was performed for the primary endpoint of the IKDC subjective score improvement at the 12-month follow-up. From a pilot study, a standard deviation of 15.2 points was found. With an alpha error of .05, a beta error of .2, and a minimal clinically significant difference of 6.7 points corresponding to one-third of the documented mean improvement, the minimum sample size was 83 for each group. Considering a possible dropout rate of 15%, 96 patients per group were required, for a total of 192 patients who were effectively enrolled (Figure 1).

Results Analysis. All continuous data were expressed in terms of the mean and the standard deviation of the mean; the categorical data were expressed as frequency and percentages. The Kolmogorov-Smirnov test was performed to test normality of continuous variables. The repeated-measures general linear model (GLM) with Sidak test for multiple comparisons was performed to assess the differences at different follow-up times of all the clinical scores and objective measures performed. The repeated-measures GLM was also used as multivariate analysis to assess the influence of the treatment on the follow-up evolution of all the clinical scores and objective measures performed. The Friedman nonparametric test, followed by the Wilcoxon post hoc pairwise comparison corrected by Bonferroni method for multiple comparisons, was used to test the differences at different follow-up times of the Tegner score. Analysis of variance (ANOVA) was performed to assess the between-group differences of continuous, normally distributed and homoscedastic data; the Mann-Whitney test was used otherwise. The GLM was used as multivariate analysis to assess the influence of the treatment on the score improvement corrected for sex, age, body mass index (BMI), symptom duration, and Kellgren-Lawrence score. The Spearman rank correlation was used to assess correlations between clinical outcome and age, BMI, and symptom duration. The Kendall tau correlation was used to assess correlations between clinical outcome and Kellgren score. The Pearson chi-square test evaluated by exact methods for small samples was performed to investigate the relationships between grouping variables. For all tests, $P < .05$ was considered significant. All statistical analysis was performed using SPSS v 19.0 (IBM Corp).

RESULTS

Patient groups were homogeneous for all the parameters except for age, which was significantly lower in the PRP group ($P = .024$) (Table 1). Nine patients (7 treated by HA and 2 by PRP injection) could not be included in the analysis due to lack of complete data at final evaluation (Figure 1).

PRP Group

No severe adverse events were reported.

A statistically significant improvement in all clinical scores was documented. In particular, the IKDC subjective score increased from 52.4 ± 14.1 to 63.2 ± 16.6 at 2 months ($P < .0005$) and remained stable for up to 12 months (66.2 ± 16.7; P = nonsignificant vs 2 months) (Figure 2). Similarly, an increase was recorded in all KOOS subscales (Table 2). The evaluation of sport activity level through the Tegner score showed a significant improvement from pretreatment (2.9 ± 1.3) to 2 months (3.6 ± 1.4; $P <$ .0005) and then values were stable up to the final follow-up (3.7 ± 1.3; P = nonsignificant), although it was not possible to regain the same preinjury level (5.2 ± 1.9). The EQ-VAS score for general health revealed a significant increase from baseline to the 12-month follow-up (73.2 ± 12.0 vs 77.6 ± 11.1; $P = .006$). A significant reduction in transpatellar circumference was also observed from the baseline evaluation to 12-month follow-up (410 ± 34 vs 402 ± 33 mm; $P = .001$), whereas no significant changes occurred in knee ROM at any follow-up.

No correlation was documented, in this group of patients, between clinical outcome and the grade of articular degeneration. Furthermore, no correlation was found

TABLE 1
Demographics of Patients Included in the Treatment Groups[a]

	PRP Group (n = 94)	HA Group (n = 89)	*P* Value
Sex, male:female, n	60:34	52:37	ns
Age, y, mean ± SD	53.32 ± 13.2	57.55 ± 11.8	.026
BMI, mean ± SD	26.6 ± 4.0	26.9 ± 4.4	ns
Symptom duration, mo, mean (range)	65.5 (4-360)	68.4 (4-300)	ns
Previous treatment, n			ns
None	12	7	
Nonoperative	29	34	
Surgical	53	48	
Kellgren-Lawrence score, mean ± SD	2.0 ± 1.1	2.0 ± 1.1	ns
Baseline IKDC subjective score, mean ± SD	52.4 ± 14.1	49.7 ± 13.0	ns
Baseline Tegner score, mean ± SD	2.9 ± 1.3	2.8 ± 1.3	ns

[a]BMI, body mass index; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; ns, nonsignificant; PRP, platelet-rich plasma.

between clinical outcome and the number of platelets or platelet concentration rate of PRP.

HA Group

Two patients reported severe pain and swelling after the first HA injection, which led them to withdraw from the injective treatment.

A statistically significant improvement in all clinical scores was found (Table 2). In particular, the IKDC subjective score increased from 49.6 ± 13.0 to 63.6 ± 15.2 at 2 months ($P < .0005$) and remained stable for up to 12 months (64.2 ± 18.0; P = nonsignificant vs 2 months) (Figure 2). Similarly, an increase was recorded in all KOOS subscales (Table 2). The Tegner score showed a significant improvement from pretreatment level (2.8 ± 1.3) to 2 months (3.3 ± 1.5; $P < .0005$) and then remained stable up to the final follow-up (3.4 ± 1.5; P = nonsignificant) but without reaching the preinjury value (4.9 ± 1.7). No significant variation was reported in the EQ-VAS score. A statistically significant reduction in transpatellar circumference was observed from the baseline evaluation to the final follow-up (415 ± 35 vs 406 ± 34 mm; $P = .002$), whereas no significant changes occurred in the knee ROM at any follow-up. No correlation was documented, in this group of patients, between clinical outcome and the grade of articular degeneration.

PRP vs HA

PRP injections produced significantly more postinjection swelling and pain with respect to HA (Figure 3). However, these reactions were self-limiting and lasted for just a few days, requiring no medical intervention. With regard to the clinical outcome, both treatments proved to be effective in improving knee functional status and reducing symptoms, but the comparative analysis showed no significant intergroup difference at any follow-up in any of the clinical scores adopted (Figure 2 and Table 2).

Furthermore, the objective evaluation of the transpatellar circumference and knee ROM with respect to the contralateral joint and in terms of changes over time did not show any difference when the measurements of the 2 treatment groups were compared. Finally, the satisfaction rate was 88.3% in the PRP group and 89.9% in the HA group.

DISCUSSION

The results of this randomized controlled, double-blind trial failed to show any benefit of PRP over HA injections for the treatment of chondropathy and early OA stages. Patients were blinded and evaluated for up to 12 months, and the outcome was analyzed at different follow-ups through several questionnaires, as well as by objective measurements. Although a significant clinical improvement was observed after treatment, no significant difference was found with respect to viscosupplementation in any evaluation performed at any of the follow-up times. Overall, the clinical benefit provided by injections was quite modest (ie, swelling reduction associated with a little symptomatic and functional improvement) for both PRP and HA administration, thus questioning the usefulness of such treatments themselves. This brings into light the debated issue regarding the effectiveness of viscosupplementation, since some recent studies have even raised questions about the real potential of HA.[24,30] Currently viscosupplementation is not officially recommended either by the American Academy of Orthopaedic Surgeons or by the Osteoarthritis Research Society International guidelines for the management of knee OA. However, the use of HA as active control in the present study could be justified by data published in favor of viscosupplementation[3] and also by ethical issues, since potentially beneficial treatment should be preferred to placebo. Moreover, HA injections are a widely applied approach for this kind of patients, and since PRP has been proposed with high expectations in the same category of patients, the comparison between PRP and viscosupplementation is particularly relevant in the clinical setting. In any case, the results of the present study are in contrast with a previous series of patients evaluated after PRP treatment and reported in the literature.[21]

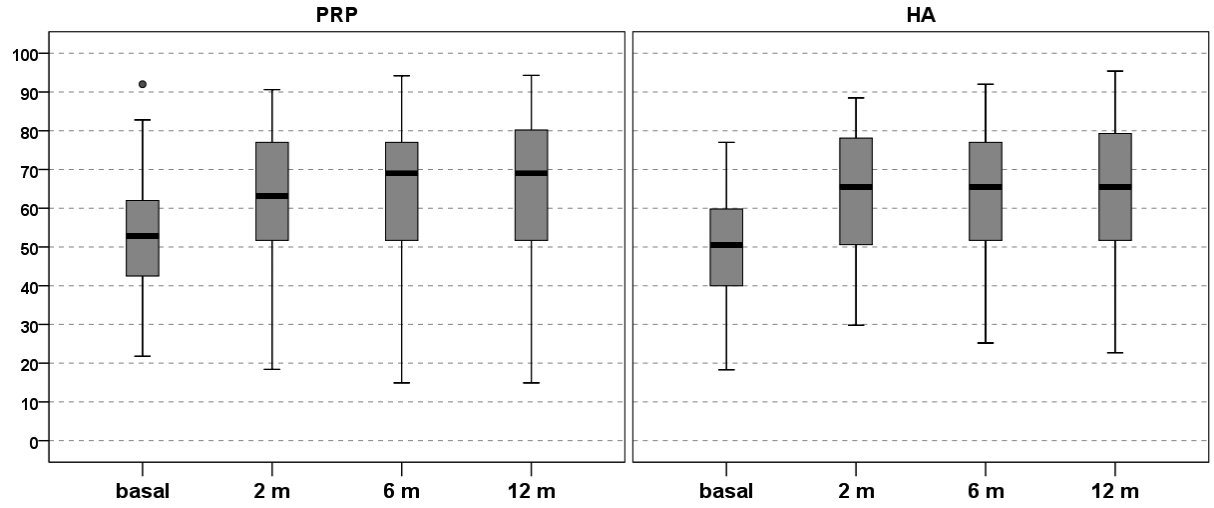

Figure 2. International Knee Documentation Committee (IKDC) subjective score trend in both treatment groups at baseline and 2-, 6-, and 12-month follow-ups. The box-and-whisker plots show median value and quartiles. HA, hyaluronic acid; PRP, platelet-rich plasma.

TABLE 2
Outcome Scores, Transpatellar Circumference, and ROM at Baseline and Follow-up in the Treatment Groups[a]

	Group	Baseline	Follow-up			*P* Value, Intergroup Difference
			2 Months	6 Months	12 Months	
IKDC subjective score	PRP	52.4 ± 14.1	63.2 ± 16.6	65.0 ± 16.1	66.2 ± 16.7	ns
	HA	49.6 ± 13.0	63.5 ± 15.2	63.5 ± 17.1	64.2 ± 18.0	
KOOS score						
Symptom	PRP	65.5 ± 16.6	72.9 ± 17.0	74.7 ± 16.9	73.9 ± 17.2	ns
	HA	65.8 ± 16.3	70.9 ± 16.6	72.7 ± 17.4	73.9 ± 18.4	
Pain	PRP	66.1 ± 17.9	73.8 ± 19.9	74.7 ± 19.3	74.9 ± 19.3	ns
	HA	64.1 ± 16.5	72.6 ± 17.9	74.8 ± 17.6	75.4 ± 19.0	
ADL	PRP	70.6 ± 19.4	79.0 ± 19.8	79.1 ± 19.6	78.4 ± 20.7	ns
	HA	68.2 ± 20.2	78.0 ± 17.9	78.4 ± 18.6	78.4 ± 19.3	
Sport	PRP	37.9 ± 25.0	48.0 ± 26.1	49.6 ± 28.6	49.3 ± 28.6	ns
	HA	35.7 ± 24.6	44.0 ± 25.5	45.1 ± 27.0	46.3 ± 28.1	
QOL	PRP	36.0 ± 19.4	48.4 ± 23.1	49.2 ± 23.4	50.8 ± 24.0	ns
	HA	35.7 ± 18.2	47.7 ± 22.1	49.9 ± 23.1	50.9 ± 24.4	
EQ-VAS score	PRP	73.2 ± 12.0	76.3 ± 12.7	76.2 ± 12.9	77.6 ± 11.1	ns
	HA	71.6 ± 13.4	73.9 ± 13.7	74.1 ± 15.1	73.4 ± 15.2	
Tegner score	PRP	2.9 ± 1.3	3.6 ± 1.4	3.7 ± 1.5	3.7 ± 1.3	ns
	HA	2.8 ± 1.3	3.3 ± 1.5	3.5 ± 1.5	3.4 ± 1.5	
ROM, deg	PRP	129.6 ± 12.2	130.6 ± 11.8	130.3 ± 10.7	130.2 ± 11.1	ns
	HA	128.2 ± 12.2	129.0 ± 10.9	128.0 ± 11.4	127.4 ± 12.0	
Transpatellar circumference, mm	PRP	410.0 ± 34.3	411.4 ± 35.2	407.2 ± 35.6	402.3 ± 33.4	ns
	HA	415.0 ± 34.7	413.3 ± 34.1	408.7 ± 32.5	406.4 ± 33.6	

[a]ADL, activities of daily living; EQ-VAS, EuroQol visual analog scale; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; ns, nonsignificant; PRP, platelet-rich plasma; QOL, quality of life; ROM, range of motion.

Preliminary studies showed that PRP intra-articular injections are safe and have the potential to reduce pain and improve knee function and quality of life, especially in younger patients with a low degree of articular degeneration.[14] Other studies have also focused on the comparison of PRP and viscosupplementation. The first comparative study was published by Kon et al[21] in 2011. PRP was tested against low- and high-molecular-weight HA in 3 groups of 50 patients, and a better performance at 6 months' evaluation was documented in PRP group. In particular, PRP produced superior results in the "chondropathy" group without OA, and patients aged up to 50 years old had

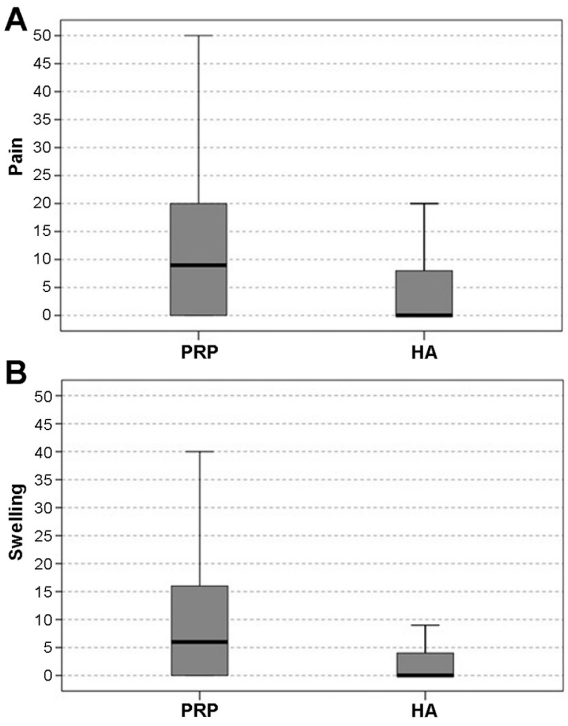

Figure 3. Post-injection pain and swelling after platelet-rich plasma (PRP) or hyaluronic acid (HA) treatment. Pain and swelling levels were obtained by multiplying the mean post-injection pain (on a 0-10 visual analog scale) by the mean duration of the episode (in days). The box-and-whisker plots show median value and quartiles.

a greater chance to benefit from PRP. Spaková et al[33] compared the efficacy of PRP versus viscosupplementation in 120 patients: an increase in clinical scores was reported in both groups, with superior results in the PRP group at 6 months. Similar results were shown in another cohort of 90 patients by Say et al,[32] who also suggested the cost-effectiveness of the procedure.

Although promising results have been obtained in several case series and benefit has been suggested by comparative nonrandomized studies,[14] only 5 randomized trials have been performed to assess the benefit offered by PRP. Sánchez et al[31] investigated the efficacy of leukocyte-free PRP compared with HA in 153 patients at 6 months of follow-up and concluded in favor of knee injective treatment with PRP. However, the only clear advantage of PRP was the number of patients with at least 50% pain reduction, whereas the study failed to show that PRP was more effective than HA. Similar results on 96 patients treated with the same blood derivative were documented by Vaquerizo et al,[36] who performed a randomized but not blinded trial against HA. The efficacy of PRP versus HA was also suggested by Mei-Dan et al[27] in osteochondral talar lesions on 30 patients: at 28 weeks, a superior clinical performance was documented in the PRP group, but the sample size remains a major limitation of this study and results obtained in this specific ankle pathologic condition cannot be easily extended to other joints and disease conditions. The effect of platelet concentrate injections for knee OA was recently investigated by Cerza et al,[6] who treated 120 patients by either autologous conditioned plasma (ACP, a low-concentrate PRP without leukocytes) or HA. The ACP group showed significantly better performance than HA in all patients, including those affected by grade 3 OA, which is in contrast with the literature showing a correlation between outcome and disease stage. A recent randomized trial by Patel et al[28] tested PRP versus saline: 78 patients affected by knee OA were included and treated bilaterally with 1 injection of PRP, 2 injections of PRP, or 1 injection of saline. Despite the low number of patients included, a significant difference was observed between PRP and saline in terms of clinical outcome. No difference was reported among patients who received 1 or 2 PRP injections. However, although this trial showed a PRP-induced clinical improvement, the study design was not able to indicate the most appropriate application modality or the advantages with respect to other injection procedures. Finally, in a preliminary report on the cohort of patients analyzed in the current study, Filardo et al[12] reported initial results on 109 patients of a randomized trial comparing leukocyte-rich PRP and HA: no statistical intergroup difference was reported, and only a tendency toward better results for the PRP group at 6 and 12 months was found in patients affected by low-grade degeneration.

The results of this double-blind, randomized controlled trial on the largest available cohort of patients evaluated at the longest follow-up did not support findings in the literature that suggested that PRP was superior to HA, not even in the group of patients affected by low-grade OA or simple knee chondropathy. There may be several ways to explain the controversial findings with respect to the other available randomized trials and the lack of superiority of PRP compared with viscosupplementation. First, the average age of the studied patient cohort is higher than that suggested by previous studies to obtain the highest benefit from PRP injections.[21] Thus, we cannot exclude the possibility that PRP has more biological and clinical potential in patients younger than those treated in this study. Moreover, the PRP used in this trial contained leukocytes, whereas the other randomized trials showing PRP superiority studied a leukocyte-poor PRP. Concerning this, it is interesting to observe that other than 2 cases of intolerance to HA, the mean pain and swelling reaction observed after the injection was higher in the PRP group, thus supporting a possible detrimental effect of white cells. This did not appear to affect the overall good clinical results at 12 months, but leukocyte depletion might have led to better results. In fact, whereas some authors consider leukocytes as a source of cytokines and enzymes that may also be important for the prevention of infections, other authors attribute the better results to leukocyte depletion, because of the deleterious effects of proteases and reactive oxygen released from white cells.[19]

The increasing awareness of the potential of different platelet concentrates is leading to a deeper insight into the importance of preparation procedures and PRP composition. Unfortunately, only one clinical study comparing PRP preparations is currently available: 144 patients were evaluated for up to 12 months, and comparable positive results

were found with high-concentrate, leukocyte-rich PRP vs low-concentrate, leukocyte-free PRP. However, the study also underlined that the PRP-leukocyte group suffered from more swelling and pain reaction after the injections,[13] thus supporting the negative role played by leukocytes. Authors of in vitro studies are now trying to explore and optimize PRP for intra-articular use. A detrimental effect of leukocytes and red blood cells was recently reported by Braun et al.[4] Human synoviocytes were cultured for 96 hours with different blood derivatives obtained from the same 4 donors: results showed a higher rate of synoviocyte death with leukocyte-rich PRP and red blood cells, and the same concentrates also led to a higher production of proinflammatory mediators. Although the small number of donors and the experimental setting (where extreme conditions were evaluated, and concentration values of the cell components were higher and not comparable with those applied in the clinical practice) are limitations of this study, the authors clearly showed the potential deleterious effects of leukocyte-rich PRP and the need to apply the proper blood derivative to target cartilage degeneration and OA.

Two studies were conducted to directly compare 2 in vitro procedures already used in clinical practice to provide evidence of advantages and disadvantages of each approach. Cavallo et al[5] focused on the effects on chondrocytes by showing that leukocyte-poor PRP led to greater cell growth and anabolism in terms of type II collagen and aggrecan production, whereas leukocyte-rich PRP contained the highest level of growth factors and cytokines and induced a higher hyaluronan production but also promoted catabolic pathways. In a similar comparative setting focused on synoviocytes, Assirelli et al[2] confirmed that leukocyte-rich PRP can upregulate inflammatory factors (interleukin [IL]–1b, IL-8, fibroblast growth factor [FGF]–2) and down-modulate anticatabolic mediators (hepatocyte growth factor [HGF] and tissue inhibitor of metalloproteinase-4 [TIMP-4]). Conversely, leukocyte-poor PRP did not provide superior results with respect to the platelet-poor plasma, thus suggesting that the lower concentrations of platelets in the leukocyte-poor PRP may lead to a significantly lower secretion of bioactive molecules and, therefore, a lower modulation of gene expression. The in vitro tissue-specific studies cannot mirror the complexity of the joint environment, but the overall available data suggest the need to optimize the cell concentration to avoid the detrimental effects ascribed to leukocytes while increasing the beneficial properties of the platelet concentrates.

Cellularity is one of the most debated aspects of PRP treatment among authors, but several other variables have to be considered, such as the preparation procedures, activation methods, storage modalities, application protocols, and many other aspects that might be important for determining the properties and clinical efficacy of PRP.[7,9,10,20,34,35,37] In particular, with regard to storage procedures, it has been shown that freeze-thawing PRP does not impair its biological properties with respect to fresh product. However, the use of frozen PRP could be considered a potential limitation of the present trial.[29] The number of names and acronyms encountered searching for studies on this biological treatment approach (eg, PRP, PRGF, ACP, PL) clearly represents the complexity of this field and explains the difficulties in literature analysis, study comparison, and understanding of some contradictory results.[14] However, despite these difficulties, the available evidence on PRP intra-articular injections showed that they are safe and can provide clinical benefit at short-term follow-up.[11,15] New insights into the importance of technical and biological variables are now emerging[8,26] and will probably help optimize platelet concentrates for this clinical application in the future. Until a new generation of products specifically conceived for intra-articular use is developed, physicians should be aware of the current options and their potential and limitations. This study shows that leukocyte-rich PRP offers a modest clinical benefit at short term and cannot provide a greater improvement with respect to HA; therefore, PRP should not be preferred to viscosupplementation as injective treatment for patients affected by cartilage degeneration and OA.

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