Platelet-Rich Plasma Intra-Articular Injection Versus Hyaluronic Acid Viscosupplementation as Treatments for Cartilage Pathology: From Early Degeneration to Osteoarthritis

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Purpose: The aim of our study is to compare the efficacy of platelet-rich plasma (PRP) and viscosupplementation (hyaluronic acid [HA]) intra-articular injections for the treatment of knee cartilage degenerative lesions and osteoarthritis (OA). **Methods:** The study involved 150 patients affected by cartilage degenerative lesions and early and severe OA. Fifty symptomatic patients were treated with 3 autologous PRP intra-articular injections and were evaluated prospectively at enrollment and at 2- and 6-month follow-up. The results obtained were compared with 2 homogeneous groups of patients treated with HA injections. One group was treated with injections of high–molecular weight HA; the other group was treated with low–molecular weight (LW) HA. International Knee Documentation Committee and EQ VAS scores were used for clinical evaluation; adverse events and patient satisfaction were also recorded. **Results:** At 2 months' follow-up, the PRP and LW HA groups showed a similar improvement, with higher results compared with the high–molecular weight HA group ($P < .005$). At 6 months' follow-up, better results were observed in the PRP group ($P < .005$). PRP and LW HA treatments offered similar results in patients aged over 50 years and in the treatment of advanced OA. PRP showed a better performance compared with HA in younger patients affected by cartilage lesions or early OA. **Conclusions:** Autologous PRP injections showed more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function. Better results were achieved in younger and more active patients with a low degree of cartilage degeneration, whereas a worse outcome was obtained in more degenerated joints and in older patients, in whom results similar to those of viscosupplementation have been observed. **Level of Evidence:** Level II, prospective comparative study.

The societal impact of degenerative diseases such as articular cartilage pathology and osteoarthritis (OA) is steadily increasing, because of the continued rise in the mean age of the active population.[1,2] Unfortunately, articular cartilage lesions, with their inherent limited healing potential, are hard to treat and remain a challenging problem for orthopaedic surgeons and all physicians.

The regeneration capacity of cartilage is limited because of its isolation from systemic regulation and its lack of vessels and nerve supply.[3-5] Unlike most tissues, none of the inflammatory processes is available for its repair, and chondrocytes cannot migrate from an intact healthy site to the site of injury.[3,4] Biomechanical, metabolic, and biologic changes, as well as trauma and isolated chondral lesions, may lead to the loss of tissue homeostasis, resulting in accelerated degeneration of the articular surface and leading

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to end-stage arthritis. OA has a major impact on functioning and independence and ranks among the top 10 causes of disability worldwide.[6] With the population aging, the prevalence of OA is increasing, and its consequences are having a significant impact on society. Thus one of the goals of modern medicine is to extend the quality of life and years of athletic activity of the population affected by cartilage lesions and OA.

A variety of noninvasive solutions have been proposed for pain treatment, improvement in function and disability, and ultimately, modification of the course of severe cartilage lesions and OA, with variable success rates.[7] Pharmacologic management usually begins with analgesia and anti-inflammatory agents[8]; the large apparent variation in individual response to each drug, the absence of clear clinical data regarding the therapeutic potency, and the potential side effects represent limits for their administration.[9] Topical agents have only been proven useful for short-term use for mild to moderate pain in mild joint degeneration.[10] Intra-articular injections of corticosteroids, as indicated by a few studies, are only of short-term benefit for pain and function.[11] Furthermore, some evidence indicates that they are not able to change the natural history of the disease and may also have negative consequences on knee structures.[12] Glucosamine and chondroitin sulfate have not been clearly shown to be effective either, and they cannot be considered ideal agents for the treatment of pain from chronic severe cartilage degeneration or OA.[13] Among the available pharmacologic solutions, despite contradictory findings and controversies regarding its effective usefulness, intra-articular hyaluronic acid (HA) is widely applied in clinical practice, with good results reported in many studies.[14-18]

The current clinical solutions suffer from significant limitations, such as safety and effectiveness, and they are not able to completely restore the patient's mobility and quality of life. Research is studying innovative approaches of stimulating repair or replacing damaged cartilage,[19] and studies regarding tissue biology have highlighted a complex regulation of growth factors (GFs) for the normal tissue structure and the reaction to tissue lesions. In fact, the role of GFs in chondral repair is now widely investigated in vitro and in vivo.[20-22] Platelet-rich plasma (PRP) is a simple, low-cost, and minimally invasive method that allows one to obtain from the blood a natural concentrate of autologous GFs.[23,24]

The aim of this study was to explore this novel biologic approach to treat degenerative lesions of articular cartilage, analyzing and comparing them with the results obtained with another common injectable treatment, viscosupplementation, at short-term follow-up. The hypothesis was that PRP would improve symptoms and function, possibly through the release of GFs and bioactive molecules, in patients affected by knee degeneration.

METHODS

Patient Selection

Clinical experimentation of this prospective comparative study was approved by our hospital's ethics committee and internal review board, and informed consent in all patients was obtained.

The following diagnostic criteria for patient selection were used: patients affected by a unilateral lesion with a history of chronic (≥4 months) pain or swelling of the knee and imaging findings (radiography or magnetic resonance imaging [MRI]) of degenerative changes of the joint. Exclusion criteria included systemic disorders such as diabetes, rheumatic diseases, hematologic diseases (coagulopathies), severe cardiovascular diseases, infections, immunosuppression, patients receiving therapy with anticoagulants-antiaggregants, use of nonsteroidal anti-inflammatory drugs in the 5 days before blood donation (for reasons of caution, because disagreement exists on the use of concomitant nonsteroidal anti-inflammatory drugs before the PRP treatment[25]), and patients with hemoglobin (g/dl) values of less than 11 and platelet values of less than 150,000/cubic mm.

For this study, 150 consecutive patients affected by cartilage degenerative lesions (Kellgren grade 0) (Fig 1), early OA (Kellgren grade I to III), and severe OA (Kellgren grade IV) were enrolled and treated with intra-articular knee injections. In all patients radiography was performed to determine the OA grade (the joint was classified according to the most degenerated compartment). In Kellgren grade 0 patients MRI was also performed to determine the chondral lesion diagnosis. Patients without evidence of cartilage changes on MRI were excluded from the study. Symptoms were due to the degenerative knee condition and not related directly to previous trauma. One-third of the patients underwent previous knee surgery, but surgery was performed at least 1 year before the injectable treatment. Among these patients, 50 were treated with 3 autologous PRP intra-articular injections, whereas 2 homogeneous groups of patients were treated with HA

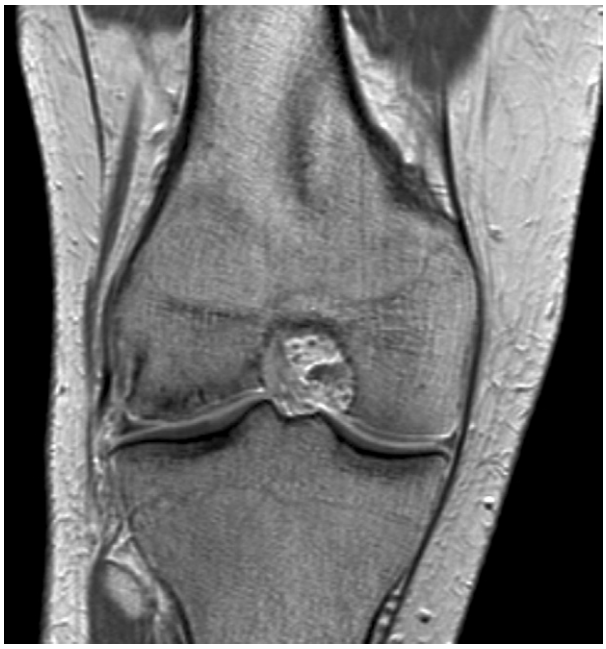

Figure 1. Coronal magnetic resonance image of a 22-year-old man with symptomatic degeneration of the articular surface at the lateral femoral condyle.

injections, 1 with high–molecular weight (HW) HA (30 mg/2 mL of HA with molecular weight 1,000 to 2,900 kDa) and the other with low–molecular weight (LW) HA (20 mg/2 mL of HA with molecular weight 500 to 730 kDa). Each group of patients received a different treatment depending on the center: every center performed only 1 treatment, and so the patient treatment allocation was determined by the center at which the patients were seen. All 3 centers enrolled consecutive patients following the same inclusion criteria. All the patients were prospectively evaluated at 2- and 6-month follow-up visits.

No statistically significant differences were found among the PRP, HW HA, and LW HA groups regarding age, sex, and previous surgery, whereas a higher body mass index was observed in the LW HA group (Table 1).

PRP Preparation and Injection

The procedure consisted of a 150-mL venous blood sample for every knee treated with PRP. A complete peripheral blood count was also collected at the time of the initial blood draw. Then, 2 centrifugations (the first at 1,480 rpm for 6 minutes to separate erythrocytes and the second at 3,400 rpm for 15 minutes to concentrate platelets) produced a unit (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. We sent 1 U to the laboratory for analysis of platelet concentration and for a quality test (platelet count and bacteriologic test), 1 U was used for the first injection within 2 hours, and the other 2 U were stored at −30°C (despite that there are no data on the effect of freezing on the clinical results of platelet injections, some studies show a nonsignificant influence on GF release, and frozen platelets have been used by several authors[26,27]). The total number of platelets per milliliter in the PRP represented a mean increase of 600% compared with whole blood values, and a mean of more than 6 billion platelets was given to the lesion site at every injection.

Injections were administered every 14 days; for the

Table 1. *Comparison of Patient Characteristics of 3 Treatment Groups*

	PRP	LW HA	HW HA	
Age (yr)	50.6 ± 13.8 (30-81)	53.2 ± 13.0 (26-75)	54.9 ± 12.6 (29-76)	NS
Sex	30 M, 20 F	27 M, 23 F	25 M, 25 F	NS
Body mass index (kg/m^2)	24.6 ± 3.2 (18-32)	26.2 ± 2.2 (20-31)	24.8 ± 3.5 (20-35)	$P = .004$
Pathology				NS
Cartilage degeneration	22	19	21	
Early OA	20	22	19	
Advanced OA	8	9	10	
Previous surgery	18 (7 meniscectomies, 6 ACL, 1 PCL, 1 patellar osteosynthesis, 4 shavings, 1 microfracture, 1 mosaicplasty, 3 second-generation ACI)	13 (12 meniscectomies, 2 ACL, 1 tibial plateau fracture osteosynthesis, 5 shavings)	17 (7 meniscectomies, 9 ACL, 2 microfracture, 5 shavings)	NS

NOTE. The groups were homogeneous except for body mass index, which was higher in the LW HA group.
Abbreviations: ACI, autologous chondrocyte implantation; ACL, anterior cruciate ligament; PCL, posterior cruciate ligament.

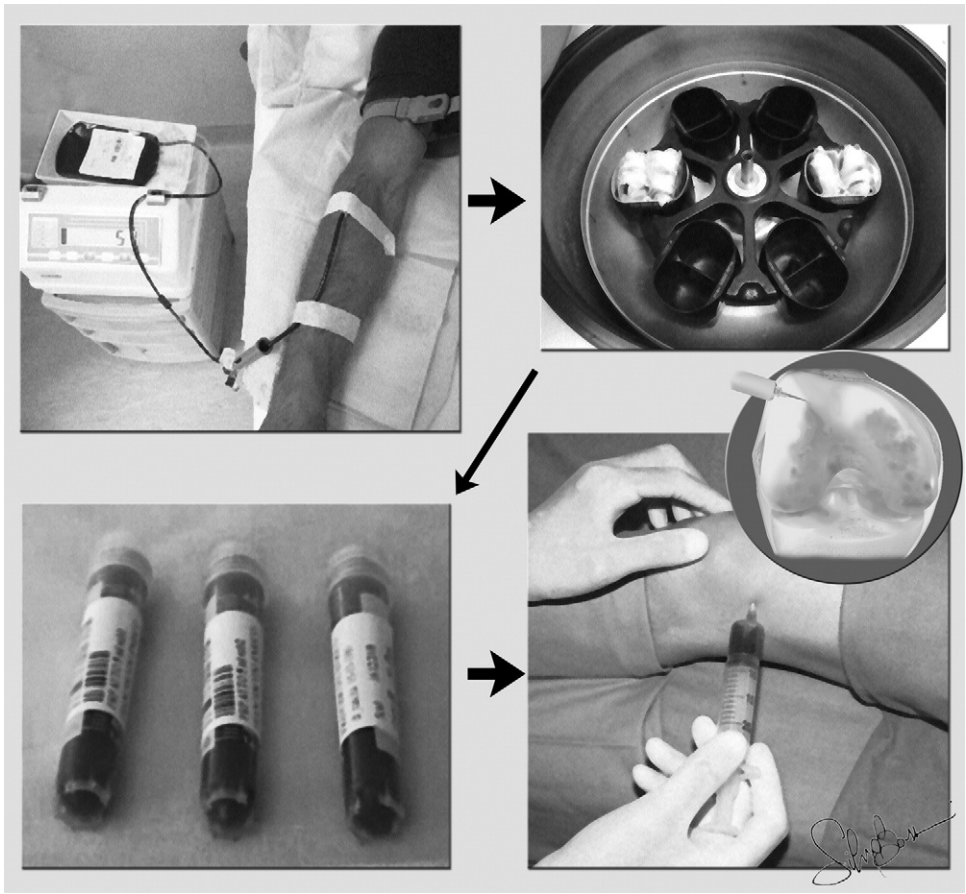

Figure 2. PRP preparation and injection procedure. A 150-mL venous blood sample is harvested for every knee treated. Then, 2 centrifugations produce small units of 5 mL each. The skin is sterilely dressed, and the infiltration is performed through a classic lateral approach with a 22-gauge needle.

second and third treatments, the samples were thawed in a dry thermostat at 37°C for 30 minutes just before application. Before the injection, 10% calcium chloride (Ca++ = 0.22 mEq × dose) was added to the PRP unit to activate platelets. The skin was sterilely dressed, and the infiltration was performed through a classic lateral approach with a 22-gauge needle. At the end of the procedure, the patient was encouraged to bend and extend the knee a few times to allow the PRP to distribute itself all over the joint before becoming a gel (Fig 2).

Postprocedure Protocol and Follow-up Evaluation

There was not a structured rehabilitation protocol; rather, a series of recommendations were made. After the injection, the patients were sent home with instructions on limiting the use of the leg and to not use nonsteroidal medication but to use cold therapy for pain for at least 24 hours. During the injection cycle, rest or mild activities (such as exercise bike or mild exercises in a pool) were indicated, and subsequently, a gradual resumption of normal sport or recreational activities was allowed as tolerated in all the treatment groups.

Patients were prospectively, clinically evaluated before the treatment and at 2- and 6-month follow-up visits. Subjective International Knee Documentation Committee (IKDC) and EQ VAS scores (as recommended by the International Cartilage Repair Society evaluation package) were used for clinical evaluation. Adverse events and patient satisfaction were also recorded.

Statistical Analysis

All continuous data were expressed in terms of the mean and the standard deviation of the mean. One-way analysis of variance was performed to assess differences among groups when the Levene test for homogeneity of variances was not significant ($P < .05$); otherwise, the Mann-Whitney test (2 groups) or the Kruskal-Wallis test (>2 groups) was used. The

least significant difference test was performed for post hoc pair-wise analysis of the Kruskal-Wallis test. A generalized linear model for repeated measures with Bonferroni correction for multiple comparisons was performed to test differences in the scores at different follow-up times. The influence of grouping variables on scores at different follow-up times was investigated by a generalized linear model for repeated measures with the grouping variable as the fixed effect. The nonparametric Pearson χ^2 test was performed to investigate the relations between grouping variables. Pearson correlation was used to assess the correlation between continuous variables.

A power analysis was performed for the primary endpoint of IKDC subjective score at the 6-month follow-up for PRP and LW HA and for PRP and HW HA. From a pilot study, an SD of 18 points was found. With an α error of 0.05, a β error of 0.2, and a minimal clinically significant difference of 10 points, the minimum sample size was 50 for each group. For all tests, $P < .05$ was considered significant.

The equivalence of a nonsignificant difference was assessed by the equivalence test according to Hoenig and Heisey,[28] considering an α level of 5% and a minimal difference of 5% of the score.

Statistical analysis was carried out by means of the SPSS software, version 15.0 (SPSS, Chicago, IL).

RESULTS

No complications related to the infiltrations were observed during the treatment and follow-up period. A statistically significant improvement in all clinical scores from basal evaluation to the 2- and 6-month follow-up visits was observed in all treatment groups (Table 2, Figs 3 and 4). These results were confirmed, including age as a covariate in the analysis.

Further analysis showed the overall worst results in patients aged over 50 years: at 6 months of follow-up, IKDC evaluation showed lower scores in older patients in the PRP group ($r = -0.399$, $P = .004$), as well as in the LW HA group ($r = -0.412$, $P = .003$) and HW HA group ($r = -0.416$, $P = .003$) (Fig 5).

The degree of knee degeneration also influenced the clinical outcome (Fig 6). In the PRP group a higher IKDC improvement at 6 months was observed in patients affected by cartilage degeneration compared with patients affected by early OA ($P = .004$) or advanced OA ($P < .0005$). In the LW HA group patients affected by advanced OA showed worse IKDC results at 2 months compared with patients affected by cartilage degeneration ($P = .001$) or early

TABLE 2. *IKDC Subjective and EQ VAS Scores at Basal, 2-Month, and 6-Month Evaluations in 3 Treatment Groups Analyzed*

	PRP			LW HA			HW HA		
	Mean ± SD (95% CI)	*P* Value*		Mean ± SD (95% CI)	*P* Value*		Mean ± SD (95% CI)	*P* Value*	
IKDC									
Basal	41.2 ± 10.9 (38.2-44.3)	Basal *v* 2 mo	<.0005	44.7 ± 6.6 (41.6-47.7)	Basal *v* 2 mo	<.0005	47.3 ± 13.9 (44.2-50.3)	Basal *v* 2 mo	<.0005
2 mo	62.7 ± 14.0 (58.7-66.7)	Basal *v* 6 mo	<.0005	61.7 ± 13.1 (57.7-65.6)	Basal *v* 6 mo	<.0005	54.8 ± 15.6 (50.8-58.8)	Basal *v* 6 mo	<.0005
6 mo	64.0 ± 18.7 (59.5-68.6)	2 mo *v* 6 mo	.99	53.8 ± 13.7 (49.2-58.3)	2 mo *v* 6 mo	<.0005	54.0 ± 16.0 (49.5-58.5)	2 mo *v* 6 mo	.3
EQ VAS									
Basal	53.6 ± 18.3 (49.8-57.3)	Basal *v* 2 mo	<.0005	51.2 ± 7.8 (47.4-55.0)	Basal *v* 2 mo	<.0005	52.2 ± 12.5 (48.4-56.0)	Basal *v* 2 mo	<.0005
2 mo	73.0 ± 13.9 (69.1-76.9)	Basal *v* 6 mo	<.0005	68.7 ± 13.5 (64.8-72.6)	Basal *v* 6 mo	<.0005	63.0 ± 14.7 (59.1-66.9)	Basal *v* 6 mo	<.0005
6 mo	72.3 ± 17.3 (68.2-77.1)	2 mo *v* 6 mo	.99	61.7 ± 14.8 (57.3-66.1)	2 mo *v* 6 mo	<.0005	62.4 ± 15.2 (58.0-66.8)	2 mo *v* 6 mo	.99

NOTE. A statistically significant improvement in all clinical scores from basal evaluation to the 2- and 6-month follow-up evaluations was observed in all treatment groups.
*With Bonferroni correction.

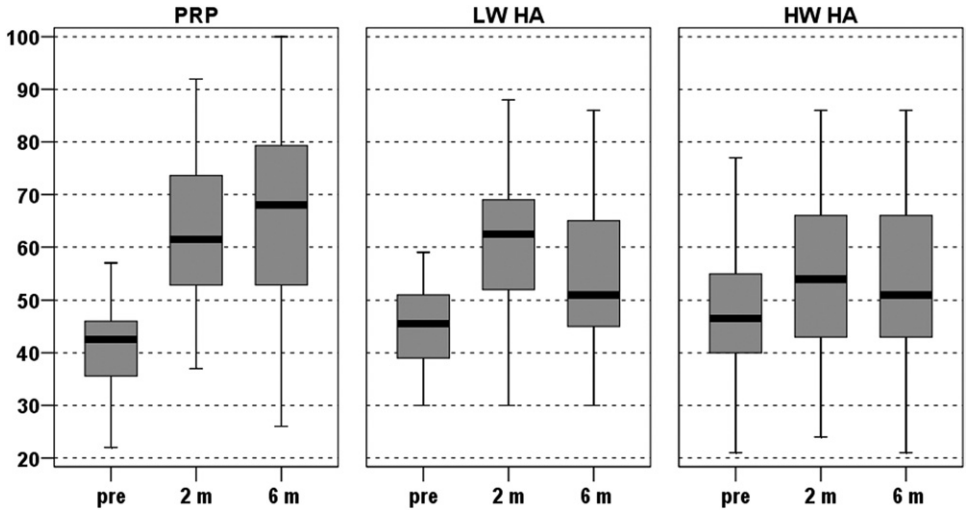

Figure 3. Health status evaluated with IKDC score (0 to 100) in the 3 treatment groups. At the 2-month evaluation (2 m), the same improvements were found in the PRP and LW HA groups, whereas lower scores were observed in the patients treated with HW HA. The analysis at the 6-month follow-up (6 m) showed better results in the PRP group compared with the LW HA and HW HA groups (black line, median; box limit, quartiles; extreme values, minimum-maximum. (pre, pretreatment.)

OA ($P = .002$). In the HW HA group higher EQ VAS results were found at 2 months in patients affected by cartilage degeneration compared with patients affected by early OA ($P = .003$) or advanced OA ($P = .05$).

Comparison of the satisfaction level obtained in the 3 groups showed a significant difference, with a higher number of satisfied patients in the PRP group (82% [41 of 50] *v* 64% [32 of 50] in the LW HA group and 66% [33 of 50] in the HW HA group; $P = .04$).

The comparison of the results also showed different findings at the 2 follow-up times. At the 2-month evaluation, the same results were found in the PRP and LW HA groups (as verified by the equivalence test, considering equivalent 2 scores having a difference of <5 points), whereas lower IKDC ($P = .009$) and EQ VAS ($P = .001$) scores were observed in the patients treated with HW HA. The analysis at the 6-month follow-up, the primary outcome of our study, showed better IKDC results in the PRP group compared with the LW HA group ($P = .003$), as well as compared with patients treated with HW HA ($P = .005$), and the same results were found with the EQ VAS (PRP *v* LW HA, $P = .001$; PRP *v* HW HA, $P = .002$).

After the 2-month follow-up (at which the same results were obtained from the PRP and LW HA groups), a significant difference was documented over time ($P = .001$), with a further improvement in the PRP group and a worsening of the results obtained in the patients treated with LW HA injections (Figs 3, 4, and 6). The analysis of the improvement from 2 to 6

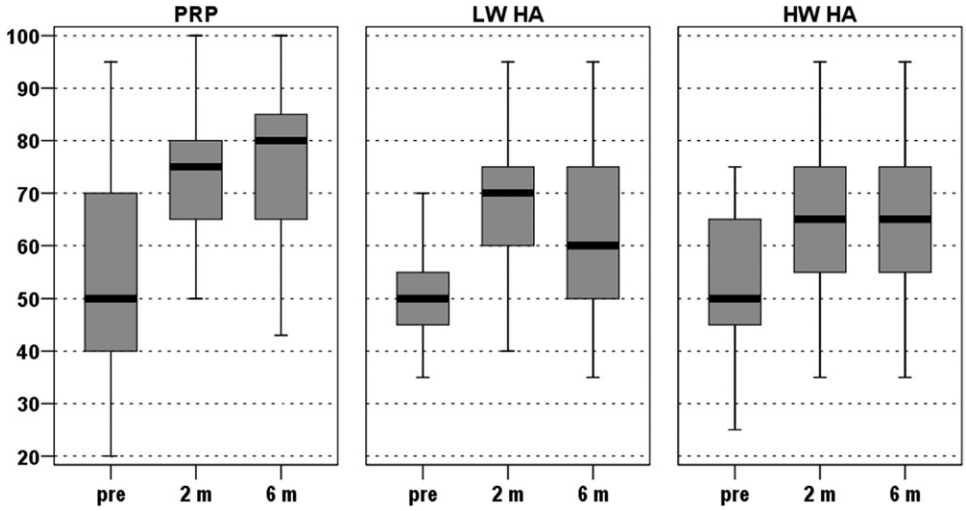

Figure 4. Health status evaluated with EQ VAS score (0 to 100) in the 3 treatment groups. At the 2-month evaluation (2 m), the same improvements were found in the PRP and LW HA groups, whereas lower scores were observed in the patients treated with HW HA. The analysis at the 6-month follow-up (6 m) showed better results in the PRP group compared with the LW HA and HW HA groups (black line, median; box limit, quartiles; extreme values, minimum-maximum). (pre, pretreatment.)

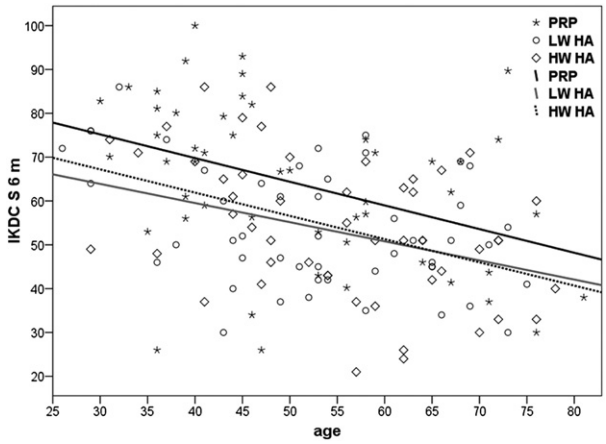

FIGURE 5. In all treatment groups age was correlated with the clinical outcome: at 6 months of follow-up (6 m), older patients obtained the worst IKDC subjective (S) results.

months showed a different trend for the different treatments for the pathology subgroup analysis. The low improvement obtained at the 2-month follow-up in the HW HA group was maintained at 6 months in all patients. Patients affected by cartilage degeneration improved further at 6 months in the PRP group, whereas those in the LW HA group worsened at 6 months. Patients affected by early OA presented stable results in the PRP group, whereas those in the LW HA group worsened. On the contrary, in the PRP group the IKDC results of patients with advanced OA worsened from the 2-month follow-up to the 6-month follow-up, whereas the group receiving LW HA injections showed more stable results in the higher degree of knee degeneration (Table 3, Fig 7).

Further analysis was performed to better analyze the influence of age on the clinical outcome obtained with the 2 treatments that showed the best results (PRP and LW HA; overall worse results were obtained with HW HA). For this purpose, we divided our patients into 2 main groups, patients aged over 50 years and those aged 50 years or younger, and in each group we analyzed the results obtained with the different procedures. The analysis of the younger patients showed the same results at 2 months (as verified by the equivalence test, considering equivalent 2 scores having a difference of <5 points), whereas at 6 months, the results found in the previous general analysis were confirmed, with a statistically significant difference ($P = .01$). The PRP group presented a further improvement in the IKDC subjective evaluation, whereas the LW HA group had marked worsening. On the contrary, older patients presented a similar trend in the 2 treatment groups, with no statistically significant difference in IKDC results at the final evaluation, even if not equivalent (Fig 8).

DISCUSSION

The results of this study showed positive effects of PRP in patients affected by knee degeneration, with an improvement of symptoms and function.

Articular cartilage lesions and degeneration are difficult to treat and present a challenge for orthopaedic surgeons because of the distinctive structure and function of hyaline cartilage and its inherent low healing potential.[3,4,5,29] For therapeutic intervention, laboratory investigations are focusing on the possibility of preserving normal homeostasis or blocking or reversing structural damage as a target to avoid, or at least delay, the need for more invasive surgical procedures.

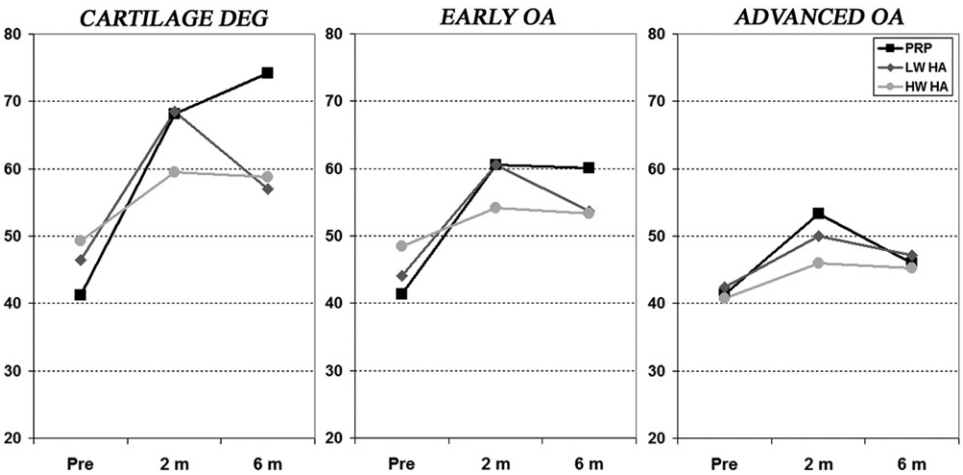

FIGURE 6. In all 3 treatment groups, patients with degenerative cartilage lesions achieved better IKDC subjective results compared with patients affected by early OA, who presented a greater improvement compared with patients with advanced OA. PRP showed superior results at the 6-month follow-up (6 m) in the cartilage degeneration (DEG) and early OA groups (2 m, 2-month follow-up). (pre, pretreatment.)

Table 3. *IKDC Subjective Scores Obtained at Basal, 2-Month, and 6-Month Evaluations in Different Knee Degeneration Degrees of 3 Treatment Groups*

	PRP [Mean (95% CI)]			LW HA [Mean (95% CI)]			HW HA [Mean (95% CI)]		
	Basal	2 mo	6 mo	Basal	2 mo	6 mo	Basal	2 mo	6 mo
Cartilage degeneration	41 (38-45)	68 (63-74)	74 (67-81)	46 (44-49)	69 (63-74)	57 (50-64)	49 (43-56)	59 (53-66)	59 (52-65)
Early OA	41 (34-48)	61 (54-67)	60 (52-69)	44 (41-47)	61 (56-65)	54 (48-60)	48 (41-56)	54 (45-63)	53 (45-62)
Advanced OA	41 (34-49)	53 (45-62)	46 (37-55)	42 (36-49)	50 (40-60)	47 (38-57)	41 (34-47)	46 (39-53)	45 (37-54)

NOTE. In all groups, patients with degenerative cartilage lesions achieved better IKDC subjective results than patients affected by early OA, who presented a greater improvement compared with patients with advanced OA.

Current pharmacologic interventions may only temporarily reduce chronic pain, but for the time being, no proven disease-modifying therapy is available.[15-17]

The use of HA injections, widely used in clinical practice and evaluated in preclinical and clinical studies, follows the rationale that arthritis involves changes in the joint surface as well as in the synovial fluid. Osteoarthritic joints have a lower-than-normal concentration of HA, so viscosupplementation delivers a preparation of HA within the joint with the goal of restoring a more normal joint fluid viscosity and improving the viscoelastic properties for proper joint mechanics. There are now several different formulations of viscosupplements produced by different manufacturers that have widely different molecular weights. The difference in molecular weight is thought to be of importance with respect to the volume/amount and number of injections, the residue time in the joint, and biologic effects. Whereas the HA effect appears to be transient, viscosupplementation has been shown to restore rheologic homeostasis in the osteoarthritic joint with improved Western Ontario and McMaster Universities Osteoarthritis Index pain and function scores by 10% to 15% at 12 months after delivery in 62% of patients.[17] Moreover, studies in the animal model have shown that intra-articular injections may inhibit cartilage degenerative changes within chondrocytes and the cartilage matrix, decrease the extent of synovial inflammation, and enhance proteoglycan content, in addition to inducing chondrogenic differentiation of embryonic mesenchymal cells, suggesting a potential role in favoring cartilage regeneration.[30,31] In the rabbit model, after treatment with microfractures, 3 HA injections had a positive effect on the repair tissue at the early follow-up time point and limited the subsequent development of degenerative changes within the knee joint,[32] and in the goat model, combined HA and marrow aspirate were shown to offer better cartilage

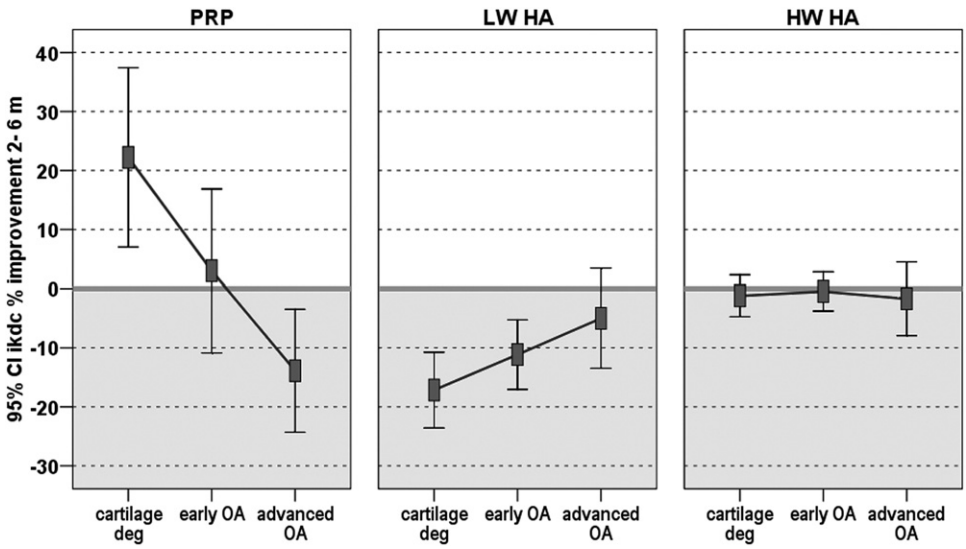

Figure 7. Trend of IKDC subjective score improvement from 2 months' follow-up (2 m) to 6 months' follow-up (6 m) for the 3 treatments analyzed in the 3 pathology subgroups: the upper part represents a further improvement at the 6-month follow-up and the gray line represents stable results, whereas the lower part represents the decrease documented in the score from 2 to 6 months' follow-up. In the PRP cartilage degenerative (deg) subgroup, a further improvement was observed from 2 to 6 months. (CI, confidence interval.)

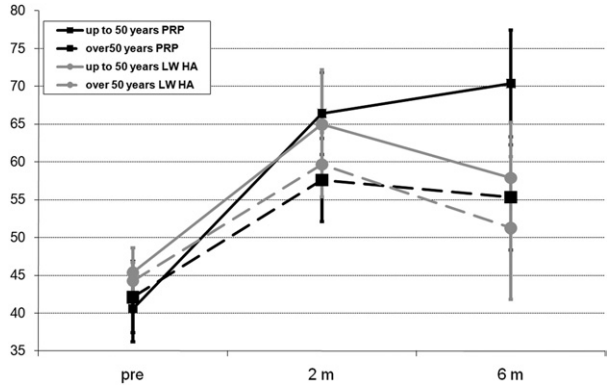

Figure 8. Age-related results showing IKDC subjective evaluation of 2 subgroups analyzed: patients aged 50 years or younger and patients aged over 50 years. In younger patients PRP was more effective at 6 months, whereas in older patients results were equivalent at both 2 months (2 m) and 6 months (6 m). (pre, pretreatment.)

repair after subchondral drilling.[33] However, although these findings and many trials showed that HA injection has beneficial effects on knee degeneration,[14,17,18] some showed that it lacks efficacy.[15,16]

Recently, 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.[15,34-38] The rationale is based on the activity of GFs carried in blood. The GFs are a diverse group of polypeptides that have an important role in the regulation of the behavior of all cells, including chondrocytes. Many GFs have been identified to take part in the regulation of articular cartilage. In particular, transforming growth factor β, one of the most important factors involved in the process of cartilage regeneration, induces chondrogenic differentiation of mesenchymal stem cells,[39] as well as matrix deposition,[20] and antagonizes most of the suppressive effects of the inflammatory mediator interleukin 1 on cartilage-specific macromolecule synthesis.[40] Platelet-derived growth factor increases chondrocyte proliferation, upregulates proteoglycan synthesis, and is a potent chemotactic factor for all cells of mesenchymal origin, including chondrocytes.[41] Insulin-like growth factor also plays an important role as an anabolic factor[42] that stimulates proliferation and proteoglycan synthesis and slows their catabolism, and it may have a role in augmenting the effects of other GFs found in cartilage.[43] Many other GFs are involved in cartilage regeneration and metabolism and may have chondroinductive actions, independently or even more with additive effects and synergistic interaction.[44]

Platelets contain in their α-granules[23] storage pools of these GFs, including platelet-derived growth factor, transforming growth factor β, insulin-like growth factor 1, and many others,[24] that have been shown to play an important role in cartilage homeostasis and to be useful for cartilage regeneration.[20-22,41,44,45] PRP is derived from the centrifugation of autologous blood and contains a platelet concentration 4 to 5 times higher than that of normal blood. The platelet concentrate is activated by the addition of calcium chloride, and this activation results in the formation of platelet gel, adhesive support that can confine the secretion of these GFs to the chosen site, with the release of a cascade of GFs.[23] The fact that platelets secrete GFs and active metabolites means that their applied use can have a positive influence in clinical situations involving tissues with a low healing potential such as cartilage.

Blood-derived GFs have already been studied for their potential in helping cartilage repair.[15,36,38,46-50] Gaissmaier et al.[47] investigated the effect of human platelet supernatant on chondrocytes in human articular biopsy specimens and observed an acceleration of chondrocyte expansion, whereas Mishra et al.[50] described how PRP enhanced mesenchymal stem cell proliferation and chondrogenic differentiation in vitro. These studies suggest an important role for these potent biologic regulators of chondrocytes in cartilage repair. However, the evidence base for clinical use of PRP is still in its infancy, and there are only a few articles that specifically address treatment applications in the orthopaedic field. In a pilot study on the treatment of knee degenerative conditions through multiple PRP injections, the analysis of 115 knees showed the safety of this procedure and a statistically significant improvement in all the parameters evaluated at short-term follow-up.[36]

The analysis of all groups of patients in this study also showed a statistically significant improvement at 2 and 6 months of follow-up, with the worst results obtained in older patients and in those with higher degrees of cartilage degeneration. However, the outcomes of the 3 groups were significantly different. The HW HA group presented the worst results at both 2 and 6 months of follow-up. Similar results were obtained at 2 months of follow-up with the PRP and LW HA injections. PRP treatment showed further improved results after the 2-month evaluation, whereas a marked worsening was observed in the LW HA group over time.

Further analysis offered a deeper explanation for this different trend. In fact, the higher results and the further improvement in the PRP group were mainly

because of the patients affected by only cartilage degenerative lesions (no OA), whereas results were stable in the patients with early OA or even worsened over time in those with advanced OA. Regarding advanced OA, the results seem to be more stable with HA injections, but this appearance is mostly because of the lower improvement achieved at 2 months. Moreover, it has to be underlined that none of these procedures showed important improvement in advanced OA (Figs 6 and 7).

The analysis of the influence of age also explains the differences between treatment groups. In fact, in the group of patients aged over 50 years, the PRP and LW HA treatments offered similar results, whereas completely different results were observed in the patients aged 50 years or younger: contrarily to the worsening documented over time in the LW HA group, a further improvement was achieved by young patients treated with PRP injections from 2 to 6 months of follow-up.

Higher results observed in young patients with a low degree of cartilage degeneration with respect to the HA treatments could be expected and easily explained by the mechanism of action hypothesized for the PRP treatment. Older and more degenerated joints present a low percentage of living and vital cells and, therefore, a low response potential to the GFs. In addition, extensive structural joint damage in severe OA is hardly reversible. Therefore the biologic changes induced by PRP may only weakly influence older joints with higher degeneration.

However, despite the lower results of this group of patients, some improvement was also observed in older patients with OA, with similar results to those offered by viscosupplementation. Another mechanism of action of PRP may be responsible for this clinical improvement. In fact, injected platelets may act at different levels, not only stimulating chondral anabolism or slowing catabolic processes. PRP may also influence overall joint homeostasis, reducing synovial membrane hyperplasia and modulating cytokine levels, thus leading to an improvement in the clinical outcome, even if only temporarily, and without affecting the cartilage tissue structure and joint degenerative progression.[46]

The limitations of this study are the lack of randomization and placebo control group other than imaging and biologic results, the primary outcome scale (appropriate for the evaluation of cartilage lesions but probably less sensitive for OA and for the older group), the evaluation of patients treated in different centers, the low number of patients treated, and the evaluation of the results only at short-term follow-up. We have analyzed our patients at a maximum 6-month follow-up because, for viscosupplementation, the treatment can be repeated after a certain time interval. In fact, most of the patients in the HA group with a tendency for worsening of the clinical outcome after 6 months have requested a second injection cycle or a different treatment, so it was not possible to further evaluate the results at a longer follow-up. Anyway, we think that the main benefit of this kind of therapy is expected with short-term follow-up.

Blinded randomized controlled studies are needed to further confirm these findings and understand the mechanism of action, determining whether there is only short-term symptom relief or whether PRP also plays a more important role through disease-modifying properties.

CONCLUSIONS

The clinical results of this comparative study suggest that this procedure may be useful for the treatment of degenerative articular pathology of the knee. Autologous PRP injections showed more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function, in particular in more active patients with a low degree of cartilage degeneration. In patients aged 50 years or younger, LW HA and PRP were more effective than HW HA at 2 months and PRP was more effective than LW HA or HW HA at 6 months, whereas in patients older than 50 years, results were equivalent at both 2 and 6 months.

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