PODCAST 5-in-5

Platelet-Rich Plasma Versus Hyaluronic Acid Injections for the Treatment of Knee Osteoarthritis

Results at 5 Years of a Double-Blind, Randomized Controlled Trial

Alessandro Di Martino,* MD, Berardo Di Matteo,†‡ MD, Tiziana Papio,§‖ BScD, Francesco Tentoni,* MD, Filippo Selleri,* MD, Annarita Cenacchi,¶ MD, Elizaveta Kon,†‡ MD, and Giuseppe Filardo,§ MD, PhD
Investigation performed at the Orthopaedic Rizzoli Institute, Bologna, Italy

Background: Platelet-rich plasma (PRP) injections have been proposed as a new conservative option for knee degeneration to provide symptomatic relief and delay surgical intervention. Although the current literature provides some evidence on the benefits of this technique compared with viscosupplementation, no studies have been performed to compare their long-term effects.

Purpose: To compare the long-term clinical outcomes provided by intra-articular injections of either PRP or hyaluronic acid (HA) to treat knee degenerative disease.

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

Methods: Patients with a history of chronic symptomatic knee degenerative changes and osteoarthritis (Kellgren-Lawrence grade 0-3) were enrolled: 192 patients were randomized to undergo 3 blinded weekly intra-articular injections of either PRP or HA. Patients were prospectively evaluated before the injection and then at 2, 6, 12, and 24 months and a mean of 64.3 months (SD, 7.8 months) of follow-up. Evaluation was based on International Knee Documentation Committee (IKDC) subjective (main outcome), EuroQol visual analog scale, and Tegner scores; 167 patients reached the final evaluation.

Results: Both treatments were effective in improving knee functional status and symptoms over time: Mean ± SD IKDC subjective score improved significantly for both PRP and HA groups ($P < .0005$) and remained stable over time up to 24 months (from 53.3 ± 14.3 to 67.3 ± 18.1 and from 50.3 ± 13.2 to 62.1 ± 20.8 for PRP and HA groups, respectively). At final evaluation, a significant IKDC reduction was observed in both treatment groups, with the PRP group still presenting significantly higher values compared with baseline: PRP 60.5 ± 19.0 ($P < .001$ vs baseline), HA 55.7 ± 18.8 (not significant vs baseline). A comparative analysis showed no significant intergroup difference in any of the clinical scores at any follow-up point. The median duration of patient subjective perception of symptomatic relief was 9 months for HA and 12 months for PRP (not significant). The only significant difference was observed in the rate of reintervention at 24 months, which was significantly lower in the PRP group (22.6% vs 37.1%, $P = .036$).

Conclusion: Both treatments were effective in improving knee functional status and symptoms over time. PRP did not provide an overall superior clinical improvement compared with HA in terms of either symptomatic-functional improvement at different follow-up points or effect duration.

Registration: NCT01670578 (ClinicalTrials.gov identifier).

Keywords: platelet-rich plasma; viscosupplementation; growth factors; intra-articular; injections; cartilage; osteoarthritis

In the past decade, interest has increased in the use of blood-derived products, based on positive in vitro findings suggesting that the delivery of platelet-derived growth factors and other bioactive molecules could delay the progression of musculoskeletal degenerative diseases, among them tendinopathies and osteoarthritis (OA).[9,12,18] In particular, the possibility of modulating the intra-articular environment by using biological products, which could reduce inflammatory distress and stimulate the anabolism of different tissues (such as cartilage, synovium, and

The American Journal of Sports Medicine
2019;47(2):347–354
DOI: 10.1177/0363546518814532

menisci), represents the rationale for the application of platelet-rich plasma (PRP) in the treatment of OA.[3,14] Despite the lack of clear recommendations, encouraging outcomes reported by preliminary clinical evidence have led many clinicians to adopt PRP in their everyday practice as a novel therapeutic option to be used as an alternative to more traditional injective treatments, such as hyaluronic acid (HA) and corticosteroids.[2] The theoretical advantages of PRP are the cocktail of concentrated bioactive molecules, its autologous nature, and the lack of side-effects typical of other common on-the-shelf pharmaceuticals. After initial enthusiasm with positive reports from several case series, randomized controlled trials (RCTs) have started to question the real effectiveness of PRP in the management of OA compared with more established treatments.[11] Although available literature shows that intra-articular PRP works better than placebo,[17,21,29,35] only a few trials have compared PRP and corticosteroids,[16,19] and no clear superiority has been documented compared with HA, which remains the most commonly used molecule for intra-articular application. Despite the increasing number of RCTs, some studies are underpowered or unblinded, thus implying low reliability of the findings.[10,24,34] A number of systematic reviews and meta-analyses have tried to shed light on this controversial point, but findings have not been fully exhaustive and are sometimes even controversial.[3,34,39] Furthermore, all trials have focused on the short-term evaluation of PRP, thus resulting in a lack of data concerning long-term outcomes, which may be a key aspect in establishing the superiority of one treatment over the other. Although no clear advantage has been demonstrated at short-term follow-up (usually 6-12 months after the injective treatment), a longer evaluation might reveal a difference between treatments in terms of clinical benefit duration. Thus, patients from a previously published RCT[11] who showed no difference between PRP and HA at short-term have been followed to 5 years to understand the evolution of their improvement over time.

The main purpose of the present double-blind RCT was to compare long-term results after intra-articular injections of either PRP or HA to treat knee OA, reporting the benefits in terms of clinical scores, effect duration, and reintervention rate for both treatments. This should indicate whether the biological approach can provide longer-lasting results compared with viscosupplementation.

METHODS

Patient Selection and Treatment

This study included the long-term follow-up of patients previously involved in a double-blind RCT[11] (2009-2013); the RCT was approved by the hospital ethics committee and scientific board, and each patient signed an informed consent form. Details concerning patient selection, randomization method, and treatment were described in a previous publication.[11] In brief, the following inclusion criteria were adopted: (1) unilateral symptomatic knee with history of chronic pain (at least 4 months) or swelling; (2) imaging findings of cartilage degenerative disease, that is, chondropathy (Kellgren-Lawrence grade = 0, detected on magnetic resonance imaging) or OA (Kellgren-Lawrence grade 1-3); (3) age between 18 and 80 years; (4) no major axial deviation (varus >5°, valgus >5°); (5) no focal chondral or osteochondral lesion; (6) absence of any concomitant knee lesion causing pain or swelling (ie, ligamentous or meniscal injury); (7) absence of hematological or cardiovascular diseases, infections, and immunodepression; and (8) hemoglobin level higher than 11 g/dL and platelet count greater than 150,000/mm^3. Four hundred forty-three patients were screened based on these criteria, and 192 of the patients were included in the trial, to be randomized into the two treatment groups: 3 weekly intra-articular injections of leukocyte-rich PRP or 3 weekly administrations of high-molecular-weight HA (Hyalubrix 30 mg/2 mL, molecular weight >1500 KDa; Fidia SpA). To keep the study blinded, all patients underwent blood harvesting to obtain autologous PRP, which was then used only in the PRP group. Before the injection, the syringe was appropriately covered to prevent patients from discovering the substance they were receiving. After the injection, patients were sent home with instructions to restrict the use of the leg for at least 24 hours and to use cold therapy or ice on the affected area to relieve pain. The RCT 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 transfusion medicine

‖Address correspondence to Tiziana Papio, BScD, Applied and Translational Research Center, IRCCS Istituto Ortopedico Rizzoli, via Di Barbiano, 1/10, 40136 Bologna (BO) Italy (email: tizianapapio@outlook.com).
*II Orthopaedic and Traumatologic Clinic, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy.
†Humanitas University, Department of Biomedical Sciences, Rozzano, Milan, Italy.
‡Humanitas Clinical and Research Center, Rozzano, Milan, Italy.
§Applied and Translational Research Center, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy.
¶Servizio di Immunoematologia e Medicina Trasfusionale, Area Metropolitana Bologna, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy.
A.D.M. and B.D.M. contributed equally to this article.
One or more of the authors has declared the following potential conflict of interest or source of funding: E.K. has received consulting fees from and has stock or stock options in Cartiheal (Israel) and has received speaking fees from Fidia (Italy), Finceramica (Italy), and Zimmer-Biomet (USA). G.F. has received consulting fees from Cartiheal (Israel), Fidia (Italy), Finceramica (Italy), and Green Bone (Italy) and has received institutional support from Cartiheal, DSM Biomedical, Fidia, Finceramica, Green Bone, IGEA Clinical Biophisic, PIRAMAL/Smith & Nephew, and Zimmer-Biomet. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

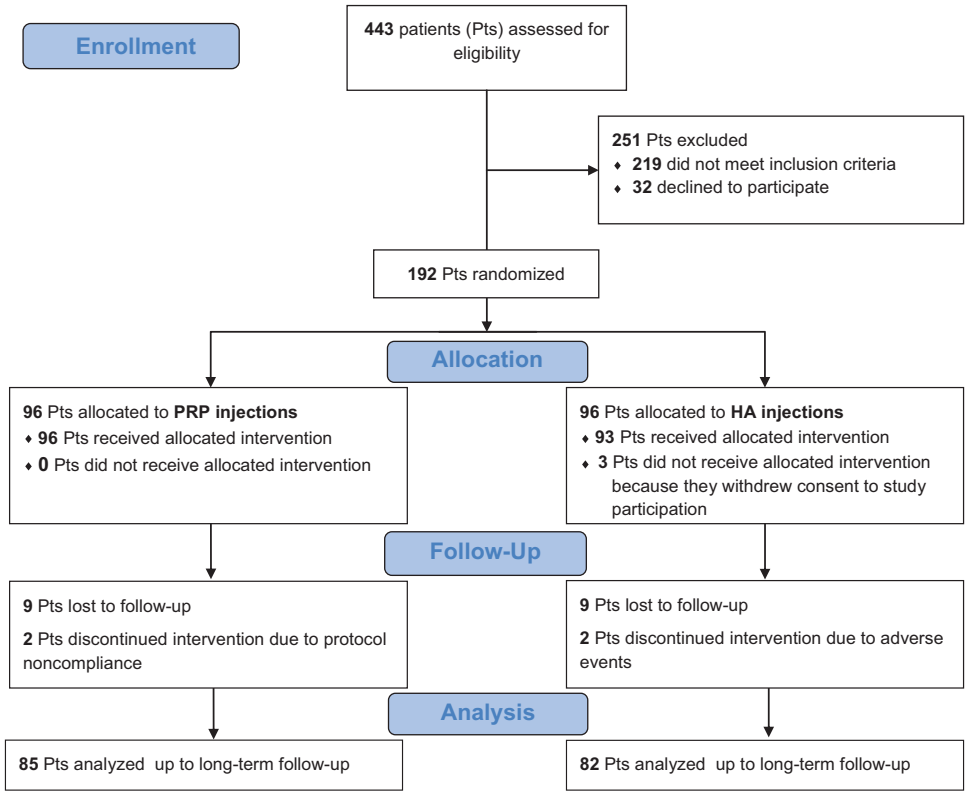

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the randomized controlled trial.

service. Two centrifugations were then performed by use of the hematology department's centrifuges: 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 units of 5 mL. One unit was sent to the laboratory for quality tests, and the remaining 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, PRP was activated by adding 10% calcium chloride. The preparation method used allowed the number of platelets to increase by a mean ± SD of 4.6 ± 1.4 times compared with baseline values. Leukocytes were also present, with a mean concentration of 1.1 ± 0.5 times compared with normal blood values.

Evaluation Tools and Follow-up

Patients were evaluated prospectively before the injection; at 2, 6, 12, and 24 months; and at a mean follow-up of 64.3 months (SD, 7.8 months) after the last injection. The following evaluation tools were used: International Knee Documentation Committee (IKDC) subjective score, visual analog scale for general health (EuroQol visual analog scale, EQ-VAS), and Tegner score. All clinical evaluations were performed by an independent physician not involved in the injective procedure. Each patient was asked to contact the referring physician by phone in case of adverse events or relapse of symptoms to determine the duration of the beneficial effect provided by the intra-articular injections. Any reintervention (ie, a new injective therapy or surgery) on the index knee during the follow-up period was assessed. Patients were kept blinded until the 1-year evaluation; afterward, their further evaluations were unblinded.

Statistical Analysis

Sample size calculation was performed as previously reported[11]: 192 patients were enrolled, considering a possible dropout of 15% and a minimum sample size of 166 patients (Figure 1). All continuous data were expressed in terms of the mean and the SD of the mean, and 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 of all the clinical scores and objective measures performed at different follow-up times. The repeated-measures GLM was also used as a multivariate analysis to assess the influence of the treatment on the follow-up evaluation 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 in the Tegner score at different follow-up times. Analysis of variance was performed to assess the between-group differences of continuous, normally distributed and homoscedastic data; the Mann Whitney test was used

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

	PRP Group (n = 85)	HA Group (n = 82)	*P* Value
Sex			NS
Male, n	53	47	
Female, n	32	35	
Age, y, mean ± SD	52.7 ± 13.2	57.5 ± 11.7	.014
Body mass index, mean ± SD	27.2 ± 7.6	26.8 ± 4.3	NS
Symptom duration, mo, mean (range)	67 (4-360)	65 (4-300)	NS
Previous treatments, n			NS
No treatment	12	6	
Nonoperative treatment	24	32	
Surgical treatment	49	44	
Kellgren-Lawrence grade, mean ± SD	2.0 ± 1.1	2.0 ± 1.0	NS
Baseline IKDC subjective score, mean ± SD	53.3 ± 14.3	50.3 ± 13.2	NS
Baseline Tegner score, mean ± SD	3.0 ± 1.3	2.8 ± 1.3	NS

[a]HA, hyaluronic acid; IKDC, International Knee Documentation Committee; NS, not significant; PRP, platelet-rich plasma.

otherwise. The GLM was used as a multivariate analysis to assess the influence of the treatment on the score improvements corrected for sex, age, body mass index, symptom duration, and Kellgren grade. Spearman rank correlation was used to assess correlation between clinical outcome and age, body mass index, and symptom duration. Kendall tau correlation was used to assess correlation between clinical outcome and Kellgren grade. The Pearson chi-square test evaluated by exact methods for small samples was performed to investigate the relationships between grouping variables. Survival analysis of the duration of the beneficial effect provided by the treatment was performed by use of the Kaplan Meier method; the log rank test was used to compare the two treatments. For all tests, $P < .05$ was considered significant. All statistical analysis was performed with 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 ($P = .014$) (Table 1).

Twenty-five patients in total (14 treated with HA and 11 with PRP injections) were excluded from the final analysis due to lack of complete data for the long-term evaluation (Figure 1).

PRP Group

A statistically significant improvement was obtained in all clinical scores. In particular, the IKDC subjective score increased from 53.3 ± 14.3 to 63.4 ± 16.7 at 2 months ($P < .0005$) and remained stable for up to 24 months (67.3 ± 18.1, *P* value not significant [NS] vs 2 months) (Figure 2).

After the 2-year evaluation, a significant reduction was observed over time, although at the final evaluation the IKDC subjective score was still significantly higher than the baseline value (60.5 ± 19.0, $P < .0005$ vs 24 months, $P < .001$ vs baseline). A similar trend was reported in the EQ-VAS score, which showed a significant increase from baseline up to 12 months of evaluation. At 24 months the EQ-VAS score was stable, and then a gradual return to the pretreatment values was observed (Table 2).

Sport activity level assessed by the Tegner score showed a significant improvement from pretreatment (3.0 ± 1.3) to 2 months (3.6 ± 1.4, $P < .0005$), and then values were stable for up to 24 months of follow-up (4.0 ± 1.2, *P* = NS), after which a gradual return to the pretreatment level was observed (3.2 ± 1.4). No correlation was documented between the level of articular degeneration or demographic factors and the clinical outcome.

HA Group

The IKDC subjective score increased from 50.3 ± 13.2 to 64.3 ± 14.7 at 2 months ($P < .0005$) and remained stable for up to 24 months (62.1 ± 20.8, *P* = NS vs 2 months) (Figure 2), after which a significant reduction was observed over time, with the IKDC subjective score gradually returning to baseline values (55.7 ± 18.8, $P < .0005$ vs 24 months, *P* = NS vs baseline). No improvement was documented in the EQ-VAS score up to 24 months of follow-up; the EQ-VAS score showed a significant decrease after 24 months, reaching lower values than the preoperative ones (baseline vs final $P = .026$) (Table 2). The Tegner score showed a significant improvement from pretreatment level (2.8 ± 1.3) to 2 months (3.3 ± 1.6, $P < .0005$) and remained stable up to 24 months of follow-up (3.4 ± 1.4, *P* = NS), after which a gradual return to pretreatment levels was documented over time (2.7 ± 1.3). No correlation was documented between the level of articular degeneration or demographic factors and the clinical outcome.

PRP vs HA

Both treatments were effective in improving knee functional status and reducing symptoms. The comparative analysis showed no significant intergroup difference at

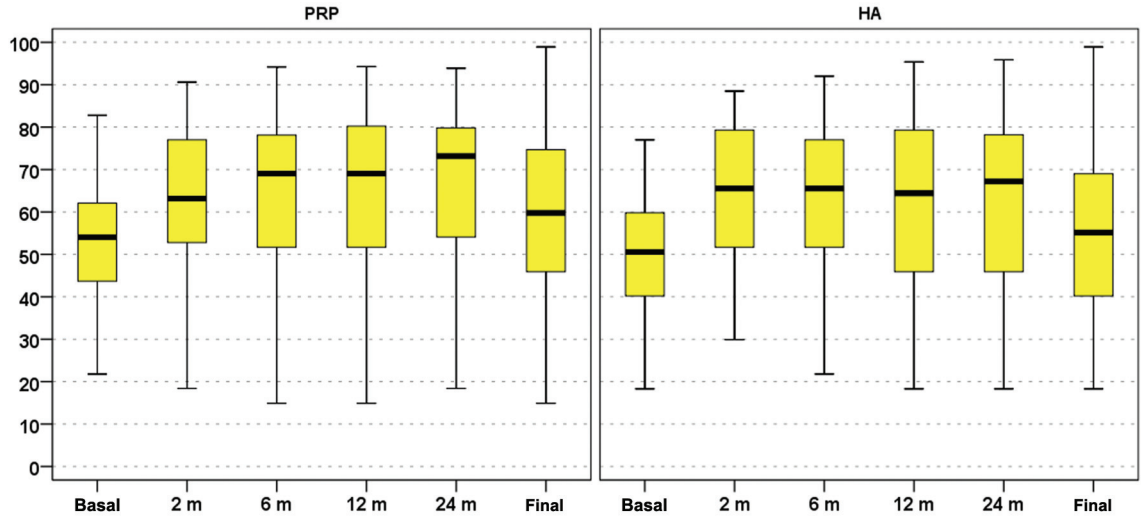

Figure 2. International Knee Documentation Committee (IKDC) subjective score trend in both treatment groups at baseline; 2, 6, 12, and 24 months; and mean 64.3 months of follow-up (box-and-whisker plot showing median value and quartiles). HA, hyaluronic acid; PRP, platelet-rich plasma.

TABLE 2
EuroQol Visual Analog Scale (EQ-VAS) Scores at Different Follow-up Times in Both Treatment Groups[a]

	Baseline	2 Months	6 Months	12 Months	24 Months	Final Evaluation
Platelet-rich plasma	72.7 ± 12.3	76.5 ± 12.7	76.9 ± 12.2	77.6 ± 10.5	79.4 ± 13.4	71.9 ± 13.6
Hyaluronic acid	71.2 ± 13.3	74.6 ± 12.8	73.8 ± 15.6	72.5 ± 15.3	74.3 ± 17.3	66.6 ± 14.2
P values	NS	NS	NS	NS	NS	NS

[a]Data are expressed as mean ± SD. NS, not significant.

any follow-up point in any of the clinical scores used (Table 2, Figure 2). Even in terms of effect duration (Figure 3), no statistically significant difference was reported between treatments: The median duration of the beneficial effect was 12 months for the PRP group (range, 9.8-13.2 months) and 9 months for the HA group (range, 4.2-13.9 months).

A significant intergroup difference was reported in the reintervention rate (ie, number of patients who underwent a new injective or surgical treatment at the index knee) within the 24 months of follow-up: HA-treated patients had a significantly higher percentage of reintervention compared with PRP patients: 37.1% (5.6% prosthesis) versus 22.6% (3.2% prosthesis), respectively (P = .036). This trend was also reported at the final evaluation, although it did not reach statistical significance (P = .063).

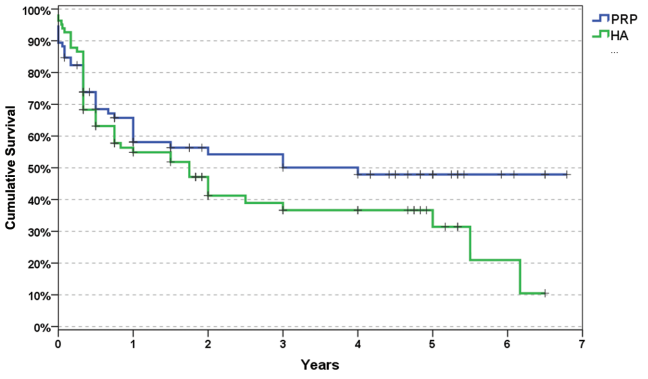

Figure 3. Survival curve of the duration of the beneficial effect provided by the injective treatments (median, 12 months for platelet-rich plasma [PRP], 9 months for hyaluronic acid [HA]). *P* value not significant.

DISCUSSION

The main finding of the present study is that there is no significant difference, in either clinical outcome or effect duration, between leukocyte-rich PRP and HA in the treatment of knee OA at long-term evaluation. Among all scores and evaluations used, the only significant difference found was in favor of PRP in the reintervention rate at 24 months, with a tendency for lower reintervention rate at the final evaluation.

This is the first double-blind RCT available on a large cohort of patients, reporting long-term data on clinical outcome, retreatment rate, and duration of symptomatic

relief, after either PRP or HA injective treatment at more than 5 years of follow-up; the presented 2- and 5-year findings are the mid- and long-term follow-up points for patients whose short-term results were previously published.[11] Clinical evaluations of RCTs published so far[3] have largely been limited to 6 or 12 months after treatment, precluding assessment of whether the biological approach might lead to a longer lasting beneficial effect. Despite the high interest in biological agents, the past decade has seen a lack of high-quality clinical research, which should have preceded the indiscriminate clinical use of these blood-derived products.[10] Most of the available RCTs have major flaws, such as being underpowered[16,26,27,29] or treating unblinded patients with the inherent risk of a placebo effect, the contribution of which may be particularly relevant in this field.[7,30,37] Of the double-blind RCTs comparing PRP versus HA, the few available studies present contradictory outcomes.[8,11,17,23,33] The overall positive, but not conclusive, results of these short-term studies leave open the question of possible differences in outcomes of these treatments over time, especially considering the different rationales for the two injective procedures. In theory, the biological approach should have a more comprehensive effect on the intra-articular tissues and should therefore lead to better results at longer follow-up times.[14]

Beyond the mere trend of clinical scores, which have been shown to increase in the short- to mid-term evaluation in all published trials, the stability of the results is equally relevant to both physicians and patients. If different treatment approaches yield similar outcomes at 6 to 12 months of evaluation, this does not mean that these treatments are absolutely equivalent. A long-term observation is required to understand whether one treatment provides more stable results over time, thus leading to a lower reintervention rate, with inherently lower risks for patients. Injective treatments are very common and can be repeated over time, but they carry the risk of infective sequelae that could be devastating[38]; therefore, products that provide long-lasting results should be prioritized by clinicians. The finding that PRP administration led to a significantly lower reintervention rate within 24 months compared with HA (partly confirmed also at final evaluation, where a tendency was observed) should be considered clinically relevant. Among these failures, only a small percentage of patients required a prosthetic intervention, attributable to both the exclusion of the highest degrees of degeneration via the study criteria and the willingness of these patients to postpone such invasive procedure by undergoing further injective procedures. This difference (detected at a later follow-up than the most common early evaluations of the injective studies at 6 to 12 months) confirms that like surgical treatments, injective treatments require long-term data on their potential effectiveness.

The findings reported in the present study do not have the strength to consider PRP clearly superior to HA, given that no significant intergroup difference was found in the overall effect duration and in the scores applied. No other differences were found in clinical scores between PRP and HA up to the evaluation at more than 60 months. However, these findings might not be representative of the potential benefit provided by other PRP treatments. PRP treatments entail several variables that could change the secreted molecules and influence the overall effect on the joint treated and the clinical benefits.[15] In this study, a freeze-thawed, leukocyte-rich PRP was used, which is different from the fresh leukocyte-poor PRP used by many of the aforementioned authors. Thus, even though neither freeze-thawing[32] nor the presence of leukocytes has been clearly proven to impair the biological effects of PRP,[25,31] these characteristics might still be responsible for different results, together with many aspects such as the activation of PRP and the use of different application protocols.[6,20] In particular, the role of leukocytes is currently the most debated aspect; authors of in vitro experiments have claimed that leukocytes stimulate the release of catabolic and proinflammatory molecules[4,36] that could be detrimental to the intra-articular environment. Nonetheless, a recent in vivo study showed that 1 week after the injection of leukocyte-rich PRP, no increase occurred in the concentration of inflammatory molecules in the synovial fluid.[25] Even though different PRP formulations could exert different effects, as established by in vitro experiments on chondrocytes and synoviocytes,[1,5,28] in vivo effects might be less predictable than suggested by in vitro tests, and the role of cellular components must still be investigated and clarified in regard to clinical outcome. The only available comparative trial revealed similar results when using leukocyte-rich and leukocyte-poor formulations,[13] leaving the question of the in vivo role of leukocytes unanswered.

Beyond the aspects related to each PRP formulation and its mode of application, the selection of the patient treated may also play a role in the observed results. In this trial, patients with different grades of cartilage degeneration (Kellgren grades 0 to 3) were included. This may have affected the results since patients with more advanced OA tend to have less benefit from PRP application, with an inherent effect on the duration of symptomatic relief.[8,22] Another limitation is the unblinding of the treatment after 1 year, which could have affected the results observed at subsequent follow-up points. Moreover, the PRP and HA groups differed in terms of age, a factor that could influence patient response to treatment. Despite these limitations, the results of this trial are relevant, being the first report in the literature of the long-term outcomes of PRP versus HA.

The long-term comparison revealed that other than a lower reintervention rate at 24 months, PRP had no clear overall superiority versus HA for the blood derivative used in this trial. Further research is needed to demonstrate whether other PRP formulations can yield more durable results than traditional treatments. In addition to providing double blinding and proper sample sizing, future studies should consider a longer follow-up period (at least 24 months) to assess fundamental aspects such as survival rate, effect duration, and need for reintervention, which could be key elements for the selection of the injective strategy to treat OA patients.

CONCLUSION

Both treatments were effective in improving knee functional status and symptoms over time. PRP did not provide an overall superior clinical improvement compared with HA, in terms of either scores evaluating symptomatic functional improvement at different follow-up points or effect duration.

ACKNOWLEDGMENT

The authors thank Dr Elettra Pignotti for statistical assistance.

REFERENCES

1. Assirelli E, Filardo G, Mariani E, et al. Effect of two different preparations of platelet-rich plasma on synoviocytes. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(9):2690-2703.
2. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46-54.
3. Bennell KL, Hunter DJ, Paterson KL. Platelet-rich plasma for the management of hip and knee osteoarthritis. *Curr Rheumatol Rep*. 2017;19(5):24.
4. Braun HJ, Kim HJ, Chu CR, Dragoo JL. The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy. *Am J Sports Med*. 2014;42(5):1204-1210.
5. Cavallo C, Filardo G, Mariani E, et al. Comparison of platelet-rich plasma formulations for cartilage healing: an in vitro study. *J Bone Joint Surg Am*. 2014;96(5):423-429.
6. Cavallo C, Roffi A, Grigolo B, et al. Platelet-rich plasma: the choice of activation method affects the release of bioactive molecules. *Biomed Res Int*. 2016;2016:6591717.
7. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med*. 2012;40(12):2822-2827.
8. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. *Am J Sports Med*. 2017;45(2):339-346.
9. Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. *Arthroscopy*. 2017;33(3):659-670.e651.
10. Dhillon MS, Patel S, John R. PRP in OA knee—update, current confusions and future options. *SICOT J*. 2017;3:27.
11. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med*. 2015;43(7):1575-1582.
12. Filardo G, Di Matteo B, Kon E, Merli G, Marcacci M. Platelet-rich plasma in tendon-related disorders: results and indications. *Knee Surg Sports Traumatol Arthrosc*. 2018;26(7):1984-1999.
13. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(10):2082-2091.
14. Filardo G, Kon E, Roffi A, Di Matteo B, Merli ML, Marcacci M. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(9):2459-2474.
15. Fitzpatrick J, Bulsara MK, McCrory PR, Richardson MD, Zheng MH. Analysis of platelet-rich plasma extraction: variations in platelet and blood components between 4 common commercial kits. *Orthop J Sports Med*. 2017;5(1):2325967116675272
16. Forogh B, Mianehsaz E, Shoaee S, Ahadi T, Raissi GR, Sajadi S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. *J Sports Med Phys Fitness*. 2016;56(7-8):901-908.
17. Gormeli G, Gormeli CA, Ataoglu B, Colak C, Aslanturk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(3):958-965.
18. Grassi A, Napoli F, Romandini I, et al. Is platelet-rich plasma (PRP) effective in the treatment of acute muscle injuries? A systematic review and meta-analysis. *Sports Med*. 2018;48(4):971-989.
19. Joshi Jubert N, Rodriguez L, Reverte-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis: a prospective, randomized, double-blinded clinical trial. *Orthop J Sports Med*. 2017;5(2):2325967116689386.
20. Kavadar G, Demircioglu DT, Celik MY, Emre TY. Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: a randomized prospective study. *J Phys Ther Sci*. 2015;27(12):3863-3867.
21. Kon E, Engebretsen L, Verdonk P, Nehrer S, Filardo G. Clinical outcomes of knee osteoarthritis treated with an autologous protein solution injection: a 1-year pilot double-blinded randomized controlled trial. *Am J Sports Med*. 2018;46(1):171-180.
22. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy*. 2011;27(11):1490-1501.
23. Lana JF, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med*. 2016;12(2):69-78.
24. Laver L, Marom N, Dnyanesh L, Mei-Dan O, Espregueira-Mendes J, Gobbi A. PRP for degenerative cartilage disease: a systematic review of clinical studies. *Cartilage*. 2017;8(4):341-364.
25. Mariani E, Canella V, Cattini L, et al. Leukocyte-rich platelet-rich plasma injections do not up-modulate intra-articular pro-inflammatory cytokines in the osteoarthritic knee. *PLoS One*. 2016;11(6):e0156137.
26. Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. *Am J Sports Med*. 2012;40(3):534-541.
27. Montanez-Heredia E, Irizar S, Huertas PJ, et al. Intra-articular injections of platelet-rich plasma versus hyaluronic acid in the treatment of osteoarthritic knee pain: a randomized clinical trial in the context of the Spanish National Health Care System. *Int J Mol Sci*. 2016;17(7):pii:e1064.
28. Moussa M, Lajeunesse D, Hilal G, et al. Platelet rich plasma (PRP) induces chondroprotection via increasing autophagy, anti-inflammatory markers, and decreasing apoptosis in human osteoarthritic cartilage. *Exp Cell Res*. 2017;352(1):146-156.
29. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;41(2):356-364.
30. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord*. 2015;8:1-8.
31. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med*. 2016;44(3):792-800.
32. Roffi A, Filardo G, Assirelli E, et al. Does platelet-rich plasma freeze-thawing influence growth factor release and their effects on chondrocytes and synoviocytes? *Biomed Res Int*. 2014;2014:692913.
33. Sanchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic

acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy*. 2012;28(8):1070-1078.
34. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res*. 2017;12(1):16.
35. Smith PA. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: an FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial. *Am J Sports Med*. 2016;44(4):884-891.
36. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med*. 2011;39(10):2135-2140.
37. Vaquerizo V, Plasencia MA, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. *Arthroscopy*. 2013;29(10):1635-1643.
38. Xu C, Peng H, Li R, et al. Risk factors and clinical characteristics of deep knee infection in patients with intra-articular injections: a matched retrospective cohort analysis. *Semin Arthritis Rheum*. 2018;47(6):911-916.
39. Xu Z, Luo J, Huang X, Wang B, Zhang J, Zhou A. Efficacy of platelet-rich plasma in pain and self-report function in knee osteoarthritis: a best-evidence synthesis. *Am J Phys Med Rehabil*. 2017;96(11):793-800.