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Clinical improvement after intraarticular and intraosseous injections of platelet rich plasma combined with hyaluronic acid for knee osteoarthritis. Case series

Mejoría clínica tras inyecciones intraarticulares e intraóseas de plasma rico en plaquetas combinado con ácido hialurónico para la artrosis de rodilla. Serie de casos

Araujo EGE,* Corral G,‡ Ochoa N,§ Torres D,¶ Gutiérrez M‖

Clínica Anglo Americana, Lima, Perú.

ABSTRACT. Introduction: knee osteoarthritis (KOA) is known as the most common form of osteoarthrosis with a 6% prevalence in people over 30 years old, and more than 40% in the population over 70 years old. The use of PRP led to diverse results and this disparity can be attributed to the dissimilar methods of PRP preparation. This study aims to assess the functional effects of intraosseous (IO) and intraarticular (IA) injections of platelet rich plasma (PRP) followed by IA injections of hyaluronic acid (HA). **Objectives:** this study aimed to assess the functional effects of intraosseous (IO) and intraarticular (IA) injections of platelet rich plasma (PRP) followed by IA injections of hyaluronic acid (HA), administered 3 and 4 weeks after the initiation of treatment in 33 patients with grade II-III (Ahlback scale) knee osteoarthritis (KOA). **Material and methods:** retrospectively, 33 patients were assessed using the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index and visual analogue scale (VAS) score. They were followed-up for 12.92 months on average. Patients were divided into three groups based on age and four groups based on the follow-up period. **Results:** the pre-operative mean of the WOMAC index was 44.35 ±

RESUMEN. Introducción: la artrosis de rodilla (OA) es conocida como la forma más común de osteoartrosis con una prevalencia de 6% en personas mayores de 30 años y más de 40% en la población mayor de 70 años. El uso de plasma rico en plaquetas (PRP) condujo a resultados diversos y esta disparidad puede atribuirse a los diferentes métodos de preparación del PRP. Este estudio tiene como objetivo evaluar los efectos funcionales de las inyecciones intraóseas (IO) e intraarticulares (IA) de plasma rico en plaquetas (PRP) seguidas de inyecciones IA de ácido hialurónico (AH). **Objetivos:** este estudio tuvo como objetivo evaluar los efectos funcionales de las inyecciones intraóseas (IO) e intraarticulares (IA) de plasma rico en plaquetas (PRP) seguidas de inyecciones IA de ácido hialurónico (AH), administrada 3 y 4 semanas después del inicio del tratamiento en 33 pacientes con osteoartrosis de rodilla (OR) grado II-III (escala de Ahlbäck). **Material y métodos:** retrospectivamente, se evaluó a 33 pacientes utilizando el índice de osteoartritis de las Universidades Western Ontario y McMaster (WOMAC) y la puntuación de la escala visual analógica (EVA). Se les realizó un seguimiento medio de 12.92 meses. Los pacientes se dividieron en tres grupos según

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* Cirujano ortopédico. Diplomado en Investigación Clínica. Clínica Anglo Americana. Formación Ortopedia TLC. Clínica Centenario. Universidad Nacional Mayor de San Marcos. Lima, Perú. ORCID: 0000-0001-7819-0113
‡ Fisioterapeuta. Artritis y Reumatología Centro Médico Imbanaco. Cali, Colombia.
§ Cirujano Ortopédico Residente. Departamento de Ortopedia, Fundación Santa Fe de Bogotá, Colombia.
¶ Cirujano Ortopédico. Especialista en Rodilla y Hombro. Departamento de Ortopedia, Clínica Anglo Americana. Educación Ortopedia TLC.
‖ Cirujano Ortopédico. Especialista en Rodilla y Hombro. Departamento de Ortopedia, Centro Médico Imbanaco. Cali, Colombia.

Correspondence:
Guillermo E Araujo
Departamento de Ortopedia. Clínica Centenario Peruano Japonesa. Universidad Nacional Mayor de San Marcos. Lima, Perú.
E-mail: guillermoaraujo127@gmail.com

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20.20 and the post-operative mean was 22.81 ± 17.25 ($p < 0.001$). The pre-operative and post-operative mean of the VAS scores were 5.79 ± 2.01 and 2.41 ± 1.43 ($p < 0.001$), respectively. The largest improvement in WOMAC (from 42.86 to 13.69) was observed in the youngest patients (44 to 55 years old) and the largest reduction in VAS (from 6.89 to 2.22) was seen in patients aged 56 to 70 years. **Conclusion:** the combination of IO and IA plasma rich in growth factor (PRGF) treatment with the IA-HA treatment yielded excellent results, diminishing pain and improving motor functionality in patients with KOA.

Keywords: knee osteoarthritis, rich in growth factor, growth factors, intraosseous infiltration, hyaluronic acid, intraarticular injection.

la edad y cuatro grupos según el período de seguimiento. **Resultados:** la media preoperatoria del índice WOMAC fue de 44.35 ± 20.20 y la media postoperatoria fue de 22.81 ± 17.25 ($p < 0.001$). La media preoperatoria y postoperatoria de las puntuaciones de la EVA fue de 5.79 ± 2.01 y 2.41 ± 1.43 ($p < 0.001$), respectivamente. La mayor mejoría en WOMAC (de 42.86 a 13.69) se observó en los pacientes más jóvenes (44 a 55 años) y la mayor reducción de la EVA (de 6.89 a 2.22) se observó en pacientes de 56 a 70 años. **Conclusión:** la combinación del tratamiento de plasma rico en factores de crecimiento (PRGF) IO e IA con el tratamiento IA-AH produjo excelentes resultados, disminuyendo el dolor y mejorando la funcionalidad motora de los pacientes con OR.

Palabras clave: osteoartrosis de la rodilla, plasma rico en factores de crecimiento, factores de crecimiento, infiltración intraósea, ácido hialurónico, infiltración intraarticular.

Introduction

Knee osteoarthritis (KOA) is known as the most common form of osteoarthrosis with a 6% prevalence in people over 30 years old,[1] and more than 40% in the population over 70 years old. Approximately 25% of the people diagnosed with KOA are not able to perform routine activities in daily life. It is estimated that, by 2050, 130 million people will be suffering from osteoarthrosis.[2] The conservative treatment for KOA includes non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, corticosteroids, hyaluronic acid (HA) intraarticular (IA) infiltrations, acupuncture, strengthening exercises, and low-impact activities (which differ widely in their indications and efficacy).[3] Recently, a novel therapy using platelet-rich plasma (PRP) has been suggested as a potential alternative. For this therapy, plasma with a high platelet concentration is obtained from the patient's blood and is combined with certain growth factors and anti-inflammatory mediators.[4] The use of PRP led to diverse results and this disparity can be attributed to the dissimilar methods of PRP preparation.[5,6,7] Widespread evidence supports the role of PRP in cell recruitment and growth owing to their anti-inflammatory properties.[8,9,10,11,12] IA application of PRP and PRGF is normally used; however, this does not affect the subchondral bone, which plays a key role in the pathogenesis and progression of KOA.[9]

In osteoarthritis (OA), the abnormal biomechanical load distribution and release of inflammatory mediators promote the failure of subchondral bone remodeling. Consequently, this decreases the remodeling of the cartilage surface. Channels and vessels of the subchondral bone provide nutritional support to the cartilage. Intraosseous (IO) PRGF might suppress the inflammatory cascade by inhibiting the nuclear factor-kappa B (NF-κB) pathway.[13] Thus, the serum levels of tumor necrosis factor-alpha (TNF-α) and inflammatory interleukins tend to decrease, resulting in the inhibition of oxidative stress.[14] In addition, PRGF may reduce the expression of transforming growth factor-beta (TGF-β), thus preventing the mesenchymal stem cells (MSCs) in the subchondral layer from becoming senescent.[15] Through these mechanisms, the subsequent remodeling of subchondral bone and reduction of angiogenesis restore homeostasis in the subchondral bone-articular cartilage unit, thereby slowing the progression of OA. Additionally, in the pathogenesis of OA, the serum concentrations and molecular weight of endogenous HA decrease due to the overproduction of free radicals and HA joint effusion.[16] This creates lower viscoelasticity in the synovial fluid, propagating the overloading force to the cartilage surface.[17] In addition, HA visco-supplementation to normal levels has several anti-inflammatory and anti-angiogenic effects.[18] Therefore, the use of PRP or PRGF in combination with HA is beneficial due to their complementary mechanisms of action.[19]

Recently, Sanchez and colleagues compared the use of IA PRGF versus IO-IA PRGF, using a fluoroscopy guide, and reported clinical advantages in the IO-IA group at 6- and 12-months follow-up.[20] This study aimed to assess the functional improvement and pain relief in patients with grade II-III (Ahlback scale) KOA treated with IO and IA injections of PRGF followed by IA injections of HA 3 and 4 weeks after initiation of treatment *(Figure 1)*. This study aims to assess the functional effects of intraosseous (IO) and intraarticular (IA) injections of platelet rich plasma (PRP) followed by IA injections of hyaluronic acid (HA), administered 3 and 4 weeks after the initiation of treatment.

Material and methods

Data of 75 patients treated with IO PRP from July 2017 to October 2018 were compiled from clinical records. The following inclusion criteria were used: (A) KOA grade II-

III (Ahlback scale); (B) ineffective previous conservative treatment; (C) approved verbal informed consent. The following exclusion criteria were used: (A) bilateral KOA requiring treatment in both knees; (B) severe mechanical malalignment (varus of 4º and/or valgus of 16º); (C) open surgery or arthroscopy within one year; (D) IA infiltration of HA or corticoid in the past 6 months; (E) body mass index above 33; (F) autoimmune rheumatic diseases and blood disorders; (G) immunosuppressive therapy, (H) anticoagulant therapy and type:[21] (I) use of corticoids or NSAIDs in the 2 weeks before treatment. Finally, 20 patients with patellofemoral OA were excluded and ten patients did not meet the criteria.

A total of 45 patients met the criteria, and 12 of them could not be contacted *(Figure 1)*. The remaining 33 patients were assessed using the WOMAC score validated in Spanish and the Visual Analogue Scale (VAS) score for pain measurement (on a scale of 0-10, where 0 = no pain and 10 = the worst pain).[22] The data were collected over the phone in September 2019 and stored in an electronic spreadsheet (Excel 2016, Microsoft, Redmond, WA, USA). The mean age and mean body mass index were 65.67 ± 10.01 years and 27.09 ± 3.6 kg/m^2, respectively, and 75.75% (n = 25) of the patients were women. All the patients were diagnosed with KOA grade II-III according to the Ahlbäck scale and followed-up for an average time of 12.92 ± 4.29 months (range 4-19 months).

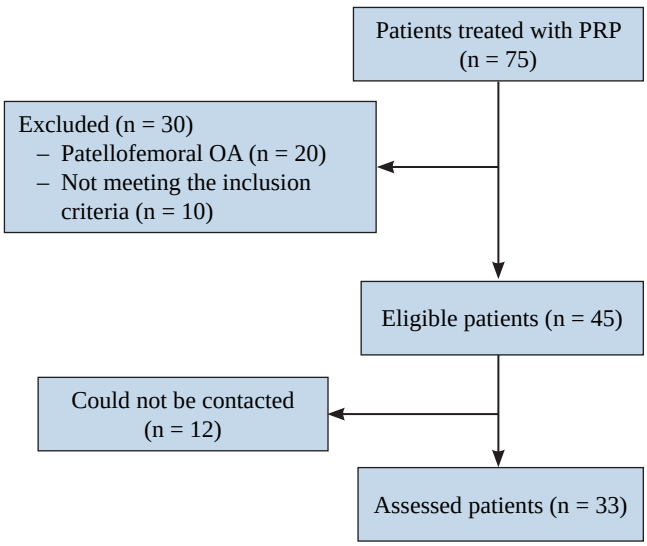

Figure 1: Flow chart of patient selection.

The categorical variables (gender and grade of KOA) were expressed as frequency, and the continuous variables (age, VAS scores, and WOMAC scores) were expressed as the mean and standard deviation. For the sake of convenience in analysis, the patients were divided by age (40 to 55, 56 to 70, and 70+) and post-operative follow-up time (4 to 7, 8 to 11, 12 to 15, and 16 to 19 months). Comparisons of pre-operative and post-operative WOMAC and VAS scores were performed using Student's *t*-test for paired-samples parametric data after assessing the normal distribution and equal variance of the samples using Shapiro-Wilk and Bartlett's tests. Data were considered statistically significant when $p < 0.05$. Statistical analysis was performed with STATAtm 13 (StataCorp, TX, USA).

To obtain the necessary PRP-Endoret®, 18 ml of venous blood was withdrawn from each patient into three tubes containing 3.8% (w/v) sodium citrate. The extracted blood was centrifuged at 580 g for 8 min at room temperature in a BTI Biotechnology Institute system centrifuge. From each tube, approximately 2 ml volume was collected from the plasma fraction located just above the sedimented red blood cells, not including the buffy coat. To initiate the activation of plasma, calcium gluconate (10% w/v) was added to the final PRGF solution immediately before injection.[23] All procedures were performed under sterile conditions.

In the first intervention, single injections of both IA PRP and IO PRP were administered under spinal anesthesia. While PRP was prepared, an arthroscopy was performed to clean and dry the joint. Next, ultrasonographic guidance was used for the IO injection of 5 ml of PRP into the medial plateau and femoral condyle (2.5 ml each) with a 13G trocar used for bone biopsy *(Figure 2)*. Traditionally, the IO injection is performed under fluoroscopic guidance.[8,20,24,25,26] However, an ultrasonography technique using the meniscus as a reference was used, as previously described by Delgado and colleagues.[9] This technique requires the trocar to be introduced 1.5 cm into the bone approximately 2 cm proximal and distal from the articular line at an angle of 45º and 30º for tibial and femoral injection, respectively *(Figure 3)*. This was followed by a 3 ml IA infiltration of

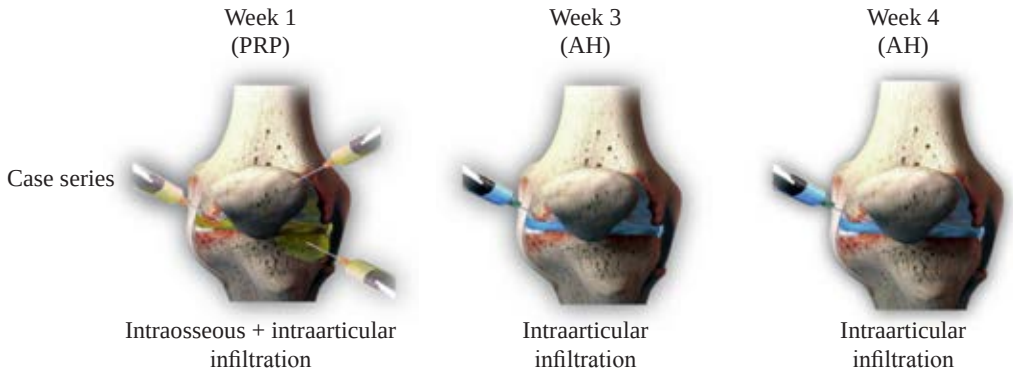

Figure 2:

Schematic representation of the treatment in this case series. Application of (IO) and intraarticular (IA) injections of platelet rich plasma (PRP) followed by IA injections of hyaluronic acid (HA), administered 3 and 4 weeks after the initiation of treatment.

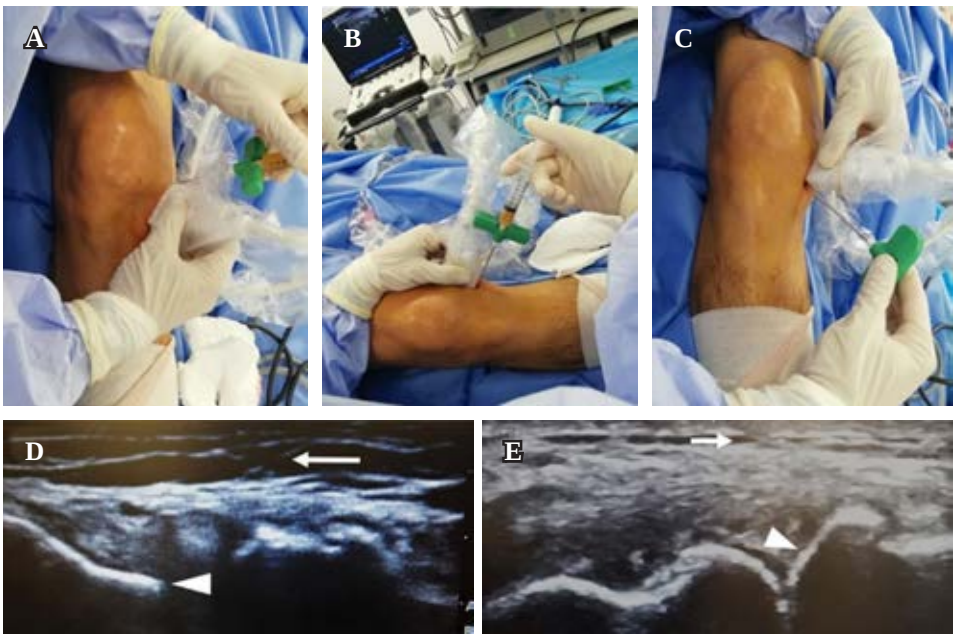

Figure 3: Intraosseous (IO) infiltration of the right knee. **A)** Infiltration into the medial femoral condyle. Notice the inclination of 30º. **B)** IO infiltration of PRGF. The ultrasound machine is placed on the contralateral side of the surgeon. The transductor probe is covered with a sterile cover (same as the arthroscopy camera) with gel on the inside. **C)** Trocar insertion into the medial tibial plateau at a 45º inclination. **D)** Ultrasonographic view of the medial femoral compartment. The needle (arrow) was introduced 1.5 cm below the medial femoral condyle (arrowhead). **E)** Ultrasonographic view of the medial tibial compartment. The needle (arrow) was introduced 1.5 cm below the medial tibial plateau (arrowhead).

PRP performed into the suprapatellar bursa. Lastly, two IA infiltrations of HA DROPYAL® were performed in the third and fourth post-operative weeks.

This study was approved by the institutional research ethics committee and conformed to the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. Images of the procedure were taken after acquiring written informed consent from the patients.

Results

Data obtained from 33 patients were analyzed. The outcomes of the therapy are summarized below and in *Tables 1 and 2*. Global improvement in motor functionality (21.54 points difference in the WOMAC index, from 44.35 ± 20.20 to 22.81 ± 17.25, $p < 0.0001$) was observed following the intervention *(Table 1)*. Similarly, an average improvement of 3.38 points in the VAS score was reported (from 5.79 ± 2.01 to 2.41 ± 1.43, $p < 0.0001$).

Significant differences in both WOMAC and VAS scores ($p < 0.05$) were observed between the pre-operative and post-operative outcomes in each age group *(Table 1)*. Also the differences exceeded the minimal clinical important difference (MCID) (Bloom 2021). The largest difference of WOMAC index (29.03 points) was observed in patients aged 40 to 55 years (from 42.86 to 13.86), while that of VAS scores was observed in patients aged 56 to 70 years (3.75 points) followed by patients aged 40 to 55 years (3.35 points).

Grouping by the post-operative follow-up time, the greatest improvement of WOMAC index was observed in the 4 to 7 months (44.38 to 19.61, 24.77 of difference) and 12 to 15 months groups (49.08 to 25.99, 23.09 of difference), while the VAS scores improved the most in the 12 to 15 months group (6.89 to 2.22, 4.67 of difference). Furthermore, the differences between pre-operative and post-operative levels of WOMAC and VAS were significant across all follow-up time groups ($p < 0.05$), and no adverse effects were reported *(Table 2)*.

Discussion

KOA is a common, progressive, and debilitating condition. Unfortunately, no effective treatments can stop or diminish its progression. PRP therapy was intended for this purpose.[4] While previous clinical studies produced inconclusive results,[6,12,23,24,27,28] some studies supported the use of IA PRP[10,29,30,31] and others supported HA application,[27,32,33] as a treatment for KOA. However, IA injection does not affect the subchondral bone that was shown to play a key role in KOA pathogenesis.[4]

This study describes the outcomes of 33 patients with KOA grade II-III (Ahlback scale), treated upon IO and IA injections of PRP followed by IA injections of HA administered 3 and 4 weeks after initiation of the treatment. No patients with KOA grade IV were included due to the diminished benefits of the therapy at this stage of the disease.[34,35] Regarding the combination of the IA injections of HA and PRP, several studies reported that it may have an enhanced effect.[17,36,37]

Prospective studies with large sample sizes also showed better post-operative WOMAC and VAS scores.[8,20] These studies have emphasized the use of IO and IA PRP over IA

Table 1: Comparison between pre-operative and post-operative outcomes, overall and by age group.

	Pre-operative, mean ± SD		Post-operative, mean ± SD		p	
	WOMAC	VAS	WOMAC	VAS	WOMAC	VAS
Age, (years)						
40-55	42.86 ± 19.78	5.21 ± 2.16	13.83 ± 12.89	1.86 ± 6.90	0.0006	0.0059
56-70	42.57 ± 20.07	6.47 ± 1.89	25.70 ± 18.32	2.72 ± 1.67	0.0052	0.0005
71 +	47.76 ± 20.76	5.23 ± 1.97	24.68 ± 17.54	2.32 ± 1.40	0.0031	0.0018
Overall	44.35 ± 20.20	5.79 ± 2.01	22.81 ± 17.25	2.41 ± 1.43	< 0.0001	< 0.0001

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. VAS = visual analogue scale. SD = standard deviation.

Table 2: Comparison between pre-operative and post-operative outcomes by post-operative follow-up time.

	Pre-operative, mean ± SD		Post-operative, mean ± SD		p	
	WOMAC	VAS	WOMAC	VAS	WOMAC	VAS
Group, (m)						
4-7	44.38 ± 24.63	5.85 ± 27.08	19.61 ± 13.48	2.10 ± 1.61	0.0253	0.0012
8-11	49.61 ± 8.34	5.13 ± 8.35	32.51 ± 17.07	3.38 ± 9.16	0.0134	0.002
12-15	49.08 ± 25.39	6.89 ± 20.89	25.99 ± 21.21	2.22 ± 17.16	0.0007	0.0007
16-19	30.21 ± 8.20	4.92 ± 9.17	10.42 ± 8.60	1.92 ± 6.65	0.0014	0.0024

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. VAS = visual analogue scale. SD = standard deviation.

injections alone. In line with these studies, we reported similar results in WOMAC and VAS scores from the beginning until 19 months post-operation. Similarly, the younger patients (40 to 55 and 56 to 70 years old) reported better results, which was apparent from the lower percentage of senescent MSCs in subchondral bone leading to early restoration of bone-cartilage homeostasis.[15,38] Grouping by post-operative time, our results were congruent with those of other studies conducted at 12 months of follow-up.[8,20] However, the 16 to 19 month follow-up group showed only minor differences between the pre-operative and post-operative WOMAC and VAS scores. This was assumed to be due to recall bias.

A recent systematic review[35] found only six studies using the IO injection method; three of them using bone substitute material and the other three using PRP or PRGF.[8,20,25] However, substantial differences between studies, the restricted number of patients, and the potential bias make it inadequate to perform a meta-analysis. This study suggests the need for further research to determine the efficacy of IO injections in early- and moderate-stage KOA.[35] Additionally, this study did not include a more recent study that reported a significant improvement in WOMAC and Knee Injury and Osteoarthritis Outcome scores following IO PRP treatment in 17 patients with KOA grade III (Kellgren-Lawrence classification).[24]

One of the strengths of our study is the use of a novel technique to treat KOA that was scarcely explored in the literature previously. Moreover, this case series involved only ultrasonographic guidance to perform the IO injection. Nevertheless, some of the limitations of this study are the small sample size and the potential recall bias emerging from the retrospective nature of the study. These limitations will be addressed in a future study with a larger sample size and controls for potential biases and confounding variables.

In summary, IO and IA PRP injections in combination with HA in this case series showed an improvement in knee functionality and KOA-associated pain in all the patients in our study. Further research is needed to elucidate the efficacy of IO-IA infiltrations of PRP combined with HA in the treatment of KOA.

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