Intraarticular injection of platelet-rich plasma in knee osteoarthritis: single versus triple application approach. Pilot study

Simental-Mendía M[1], Acosta-Olivo CA[1], Hernández-Rodríguez AN[1], Santos-Santos OR[1], de la Garza-Castro S[1], Peña-Martínez VM[1], Vilchez-Cavazos F[1]

ACTA REUMATOL PORT. 2019;44:138-144

ABSTRACT

Objective: To compare the clinical effectiveness of the triple intraarticular injection of platelet-rich plasma (PRP) with respect to the single injection in patients with mild osteoarthritis of the knee.
Methods: A total of 35 patients with a clinical and radiographic diagnosis of osteoarthritis grade I and II (according to Kellgren-Lawrence radiological scale) were analyzed. They were randomized into two groups: single application (18 patients) and triple application (17 patients). Both groups were evaluated using the Visual Analogue Scale (VAS), the Western Ontario and McMaster Universities (WOMAC) index, and the Health Survey 12v2 (SF-12) at baseline and at 6, 12, 24, 36 and 48 weeks post-treatment.
Results: Both treatments significantly decreased the level of pain (VAS) (single, from 7.3±2.1 to 4.6±2.7 and triple, from 6.6±2.4 to 0.9±1.4; $p<0.05$) and the total WOMAC (single, from 44.2±19.7 to 26.7±24.9 and triple, from 41.4±15.5 to 7.2±7.3; $p<0.05$) at the end of the study. The triple application showed better improvement in the VAS ($p= 0.0007$) and the total WOMAC ($p= 0.0209$) scores when comparing the final results between groups.
Conclusion: The triple injection of PRP in patients with mild knee osteoarthritis is clinically more effective than the single application at 48 weeks of follow-up.

Keywords: Platelet-rich plasma; Osteoarthritis; Knee; intraarticular; Injection.

INTRODUCTION

Osteoarthritis (OA) refers to a clinical syndrome of joint pain with a multifactorial etiopathogeny. It is characterized by the gradual loss of articular cartilage, osteophyte formation, subchondral bone remodeling and joint inflammation[1]. OA leads to symptoms such as pain and loss of function, mainly in the knee and hip. It affects 9.6% of men and 18% of women over 60 years. In addition, it is considered to be the most common cause of disability and pain worldwide[2].

OA of the knee is the predominant form of OA and the leading cause of disability in the United States. It is estimated that 27 million people suffer from the disease[3]. In Mexico, an average prevalence of OA in the adult population was estimated at 10.5% in 2011 in a study conducted in 5 populations in different states of the country[4].

In early OA, the initial treatment is based on the reduction of symptoms with the use of non-steroidal anti-inflammatory drugs and topical or intraarticular agents. However, these drugs have good short-term results, but do not change the natural course of the disease[5]. Recently, the use of platelet-rich plasma (PRP) as a main therapy or as a coadjuvant to the conventional treatment of musculoskeletal system pathologies has become more relevant[6]. PRP is a volume of plasma that is obtained from the blood of the same patient and holds a platelet concentration above normal limits[7]. The autologous nature of PRP offers the advantage of not generating any immunological reaction[8]. Additionally, PRP therapy has been shown to naturally stimulate the cartilage repair process by releasing the growth factors contained in the platelet alpha granules. PRP also accelerates the physiological recovery process when administered locally, providing support for cellular connections, and may be able to relieve pain[9].

The use of PRP has also shown the ability to reduce the pro-inflammatory effects of interleukin-1β (IL-1β), which is known as one of the molecules that most promotes inflammation in OA and has a major role in car-

1. Universidad Autonoma de Nuevo Leon, Orthopedics and Traumatology Service

tilage degradation, by inducing chondrocytes and synovial cells to synthesize enzymes that degrade the extracellular matrix[10,11]. In addition, one of the main growth factors with chondrogenic effects present in platelets, such as transforming growth factor beta (TGF-β), stimulates the synthesis activity of chondrocytes and decreases the catabolic activity of IL-1β[12].

Despite multiple reports, no consensus has been established about a standard regimen for PRP treatment in knee OA[6]. Various therapeutic schemes have been used in terms of the number of injections; they have been evaluated from one to three intraarticular injections of PRP[13,14]. The main objective of the present study is to determine whether the triple application of PRP has a greater therapeutic effect in the treatment of patients with knee OA grade I and II in the Kellgren-Lawrence radiological scale, with respect to the single application.

PATIENTS AND METHODS

PATIENTS AND STUDY DESIGN

Controlled, randomized, prospective and longitudinal clinical trial. Patients over 40 years of age, of indistinct gender, who had not received infiltration with steroids or medical treatment at least 2 weeks prior to the start of the protocol, with diagnosis of OA (primary) grade I and II in accordance with the radiological scale of Kellgren-Lawrence[15], were recruited in the outpatient clinic. Patients with associated rheumatic diseases, liver diseases, diabetes, coagulopathies, severe cardiovascular diseases, infections, immunosuppression, anticoagulant therapy or patients with a hemoglobin concentration <11g/dL and platelets <150,000/ L were excluded. All the included patients signed an informed consent letter, approved by the Research Ethics Committee of our institution (Registration No. OR15-002). The study was recorded in the *ClinicalTrials.gov* public database with registration number NCT02370420. Patients were randomly divided into two groups by means of a randomization plan designed with a tool available online (*randomization.com*). Patients in group 1 were given a single intraarticular injection of PRP, while patients in group 2 received three intraarticular injections of PRP within an interval of 2 weeks between each application.

PRP PREPARATION

The PRP was obtained from a sample of 45 mL of venous blood from the patient, distributed in vacutainer tubes with 0.129 M sodium citrate (369714, BD Vacutainer, Franklin Lakes, NJ, USA). An extra tube of blood sample with EDTA (Ethylenediaminetetraacetic acid) was taken as an anticoagulant to perform the initial platelet count of the patient (368171, BD Vacutainer, Franklin Lakes, NJ, USA). The samples were centrifuged for 5 minutes at 1800 rotations per minute (rpm) to separate the blood in its different cellular components. The upper layer corresponding to the plasma of each of the tubes was carefully placed in a new sterile propylene tube, taking care not to remove the buffy coat. The plasma collected from all the tubes was centrifuged again for 5 minutes at 3400 rpm to concentrate the platelets. The upper part of the centrifuged plasma was discarded due to its poor concentration of platelets (platelet poor plasma) and the lower volume of plasma (5 mL) containing the highest number of platelets (PRP) was collected. This volume of PRP was transferred to a new sterile glass tube. A sample of the final PRP was sent to the laboratory to perform the final platelet count. The manipulation of the blood samples and PRP was carried out inside a laminar flow biosafety cabinet of high efficiency Class II Type A2 to avoid any contamination (Logic A2, Labconco, Fort Scott, KS, USA).

APPLICATION PROCEDURE OF PRP

Asepsis of the knee was performed with Avagard D (3M Health Care, St. Paul, MN, USA), then local anesthesia (2 mL) was performed with 2% lidocaine hydrochloride (Laboratorios PISA, Guadalajara, México) in the conventional lateral arthroscopy portal area, which served as an intraarticular entry site. Prior to its application, the PRP was activated using 0.75 mL of a 10% calcium gluconate solution (Laboratorios PISA, Guadalajara, México).

PATIENTS FOLLOW-UP

At the end of the infiltration, bending exercises and passive extension of the knee were performed for 20 seconds to achieve an adequate intraarticular distribution of the PRP. After 10 min of observation, patients were sent home with written indications that included relative rest for the next 48 hours, application of cold for 15 minutes 3 times a day, and the intake of paracetamol (500 mg) as rescue medication. All the above only in case of pain or discomfort.

Patients in both groups were evaluated using the Visual Analogue Scale (VAS), the Western Ontario and

McMaster Universities (WOMAC) OA index, and the short version in Spanish (Mexico) of the Health Survey 12v2 (SF-12) to measure the symptomatic improvement of the patient. The evaluations were applied before the procedure and at 6, 12, 24, 36 and 48 weeks after the start of treatment. Additionally, the pain level was recorded after each injection in all the patients.

STATISTICAL ANALYSIS

We used the 80% upper confidence limit approach for sample size calculation and determined a pilot trial sample size between 20 and 40 for a main study sample size of 80-250 participants (for 90% power based on a standard sample size calculation). The normality of the data obtained was analyzed through the mean, and the variance was analyzed using the Shapiro-Wilk test. The non-parametric Chi-square and Fisher's Exact tests were used to investigate differences between the qualitative variables of both groups. To compare the variables with a normal distribution, independent *t* tests and an analysis of variance (ANOVA) were used with a *post hoc* test for multiple comparisons (Tukey test or Dunnet test). To evaluate the variables with a non-normal distribution, the nonparametric tests of Wilcoxon and Kruskal-Wallis were applied with a *post hoc* test for multiple comparisons (Dunn's test). The values of $p < 0.05$ were considered as statistically significant. The data was analyzed with the GraphPad Prism software version 5.00 for Windows. (GraphPad Software, San Diego, CA, USA). All values are expressed as mean ± standard deviation (SD).

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS INCLUDED

Of the total patients studied, 29 were female and only 6 were male. In addition, 33 of the patients presented a grade II OA according to the Kellgren-Lawrence scale. Both the age of the patients as well as their body mass index (BMI) were not significantly different between the two groups. Additionally, the mean of the initial global values of the VAS, WOMAC and SF-12 scores in both groups were similar ($p > 0.05$). The full demographic information of both groups of patients is presented in Table I.

CHARACTERISTICS OF PRP SAMPLES

An increase of up to 206.1% in the platelet concentration in the PRP of the triple application group was observed with respect to its concentration in whole blood (Table II). In the single application group, the platelet concentration in the PRP increased 208.7% with respect to the concentration in whole blood. In general, a concentration of less than 10% was observed in the presence of leukocytes in the injected PRP, with respect to the concentration of these cells in whole blood (Table II).

EVALUATION OF THE LEVEL OF PAIN ACCORDING TO THE VAS

There was a significant decrease in the level of pain in the VAS in the two treatment groups from week 6 (Figure 1), which was maintained until the end of the follow-up ($p < 0.05$). However, when comparing the final values of the VAS in both groups (single: 4.6±2.7, triple: 0.9±1.4 ; mean ±SD), it was observed that the decrease in pain sensation is greater in the triple application group ($p = 0.0007$; Table III).

TABLE I. COMPARISON OF THE BASELINE CHARACTERISTICS OF THE PATIENTS INCLUDED IN BOTH STUDY GROUPS

	Comparative demographics		
	Single injection	Triple injection	p value
Patients, (n)	18	17	
Age, mean (SD)	54.6±11.6	60.1±10.6	0.2982
Gender, female, n (%)	17 (94.4)	12 (70.6)	0.0877
BMI, mean (SD), kg/m²	29.6±5.9	31.5±4.8	0.8786
Kellgren-Lawrence			
Grade I, (n)	1	1	1.0000
Grade II, (n)	17	16	
VAS, mean (SD), 0-10 cm	7.3±2.1	6.6±2.4	0.4081
WOMAC Total, mean (SD)	44.2±19.7	41.4±15.5	0.6427
Pain, mean (SD)	9.7±3.1	9.1±3.0	0.5608
Stiffness, mean (SD)	3.7±1.7	3.2±1.9	0.3790
Functionality, mean (SD)	30.7±15.7	29.06±12.65	0.7332
SF-12 MCS, mean (SD)	51.1±8.6	51.7±12.9	0.8735
SF-12 PCS, mean (SD)	33.8±8.4	37.0±6.8	0.2353

BMI, body mass index; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index; SF-12, Health Survey 12v2; MSC, Mental Component Summary; PCS, Physical Component Summary

TABLE II. QUANTIFICATION OF PLATELETS AND LEUKOCYTES IN WHOLE BLOOD AND PLATELET-RICH PLASMA (PRP) SAMPLES

	Platelets (×10³/µL)				Leukocytes (×10³/µL)			
	Study group				Study group			
Sample analyzed	Single	Triple 1	Triple 2	Triple 3	Single	Triple 1	Triple 2	Triple 3
Whole blood, mean (SD)	239.3±49.6	236.3±41.9	237.9±38.4	235.1±37.2	5.82±1.08	6.14±1.07	6.06±1.12	6.07±1.34
PRP, mean (SD)	499.3±162.0	446.3±107.2	471.1±91.1	484.6±106.4	0.55±0.30	0.48±0.52	0.43±0.27	0.58±0.36
Change (%)	208.7	188.9	198.0	206.1	-9.5	-7.8	-7.1	-9.6

PRP, platelet-rich plasma

TABLE III. CLINICAL EVALUATIONS PERFORMED AT BASELINE AND AT 48 WEEKS POST-TREATMENT

	Single injection			Triple injection		
Scale analyzed	Baseline	48 weeks	p value	Baseline	48 weeks	p value
VAS, mean (SD), 0-10 cm	7.3±2.1	4.6±2.7[a]	0.0049	6.6±2.4	0.9±1.4[a]	<0.0001
WOMAC Total, mean (SD)	44.2±19.7	26.7±24.9[b]	0.0269	41.4±15.5	7.2±7.3[b]	<0.0001
Pain, mean (SD)	9.7±3.1	5.1±4.9	0.0431	9.1±3.0	1.9±2.0	<0.0001
Stiffness, mean (SD)	3.7±1.7	3.8±6.0	ns	3.2±1.9	0.7±0.8	0.0071
Functionality, mean (SD)	30.7±15.7	17.8±17.7[c]	0.0199	29.1±12.7	4.5±5.2[c]	<0.0001
SF-12 MCS, mean (SD)	51.1±8.6	53.6±8.8	ns	51.7±12.9	48.3±9.9	ns
SF-12 PCS, mean (SD)	33.8±8.4	42.8±9.0[d]	0.0360	37.0±6.8	52.9±8.7[d]	0.0030

VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index; SF-12, Health Survey 12v2; MSC, Mental Component Summary; PCS, Physical Component Summary; ns, p value no statistically significant.
a-Significant difference in the VAS value at 48 weeks in the treatment with triple injection with respect to the treatment with a single injection (p = 0.0007). b-Significant difference in the total value of WOMAC at 48 weeks in the treatment with triple injection with respect to the treatment a single injection (p = 0.0209). c-Significant difference in the value of the subscale of functionality at 48 weeks in the treatment with triple injection with respect to the treatment a single injection (p = 0.0259). d-Significant difference in the total value of PCS at 48 weeks in the treatment with triple injection with respect to the treatment a single injection (p = 0.0124).

EVALUATION OF THE WOMAC INDEX

The values for the Pain, Stiffness and Functionality subcategories of the WOMAC index decreased significantly at 48 weeks of evaluation with respect to the baseline values in the triple application group (Table III). In the case of the single application, only the Stiffness subcategory showed no clear improvement at week 48 (Table III). When comparing the three subcategories between both groups, only a significant difference was observed in the Functionality subcategory (p =0.0259) in favor of the triple application at 48 weeks (single, 17.8±17.7 vs. triple, 4.5±5.2; mean ±SD). We were able to identify a significant decrease in the total values of the WOMAC index when performing the comparison at 48 weeks of follow-up with respect to the baseline values in both groups (p <0.05). Importantly, the total score of the WOMAC index was significantly better in the triple injection group with respect to the single application group (p =0.0209; Figure 2, Table III).

QUALITY OF LIFE ASSESSMENT ACCORDING TO THE SF-12 SURVEY

The results of the SF-12 health survey can be grouped into two main domains: mental component summary (MCS) and physical component summary (PCS). In both groups a significant increase was observed in the average values of the PCS at 48 weeks compared to their baseline values (p <0.05; Figure 3A). Regarding the MCS, no significant changes were recorded in either of the two groups (Figure 3B, Table III). We could identify a significant improvement in the triple application

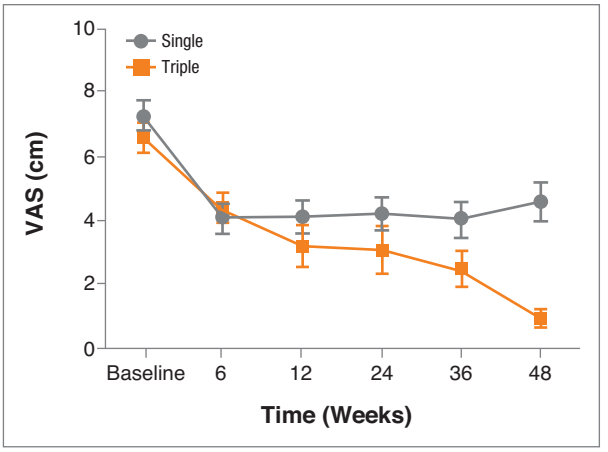

FIGURE 1. Mean (±SD) values for VAS in the single and triple PRP injection groups. The level of pain decreases significantly from week 6 and up to week 48 in the single application group (baseline 7.3 ± 2.1, 6 weeks 4.1 ± 1.9, 48 weeks 4.6 ± 2.7, p <0.05) and the triple application (baseline 6.6 ± 2.4, 6 weeks 4.3 ± 2.5, 48 weeks 0.9 ± 1.4, p <0.01). The pain level is lower in the triple application group at 48 weeks compared to the single application (p = 0.0209)

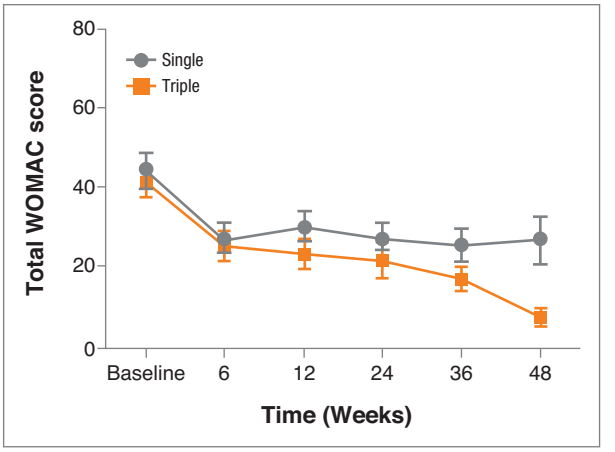

FIGURE 1. Mean (±SD) values for total WOMAC index score in the single and triple PRP injection groups. A significant decrease was observed in the total score of the WOMAC index from week 24 with the single application (baseline 44.2 ± 19.7, 24 weeks 27.4 ± 14.1, 48 weeks 26.7 ± 24.9, p <0.05) and from week 12 with the triple application (baseline 41.4 ± 15.5, 12 weeks 23.1 ± 16.1, 48 weeks 7.2 ± 7.3, p <0.01). The value of the total score was lower in the group of the triple application at 48 weeks with respect to the single application (p = 0.0007)

group when comparing the values of the PCS of both groups at 48 weeks (p <0.05; Table III).

LEVEL OF PAIN AFTER PRP INJECTION

The level of pain or discomfort after each one of the injections was recorded in all the evaluated patients. At the end of the study, more than 70% of the subjects reported nothing or little pain in the 48-h following the injection. Those patients who reported moderate or severe discomfort presented a resolution of this eventuality of no more than 72-h. None of the treated patients showed any severe adverse effect (defined as that event that required medical management additional to that previously indicated to the patient, such as hospitali-

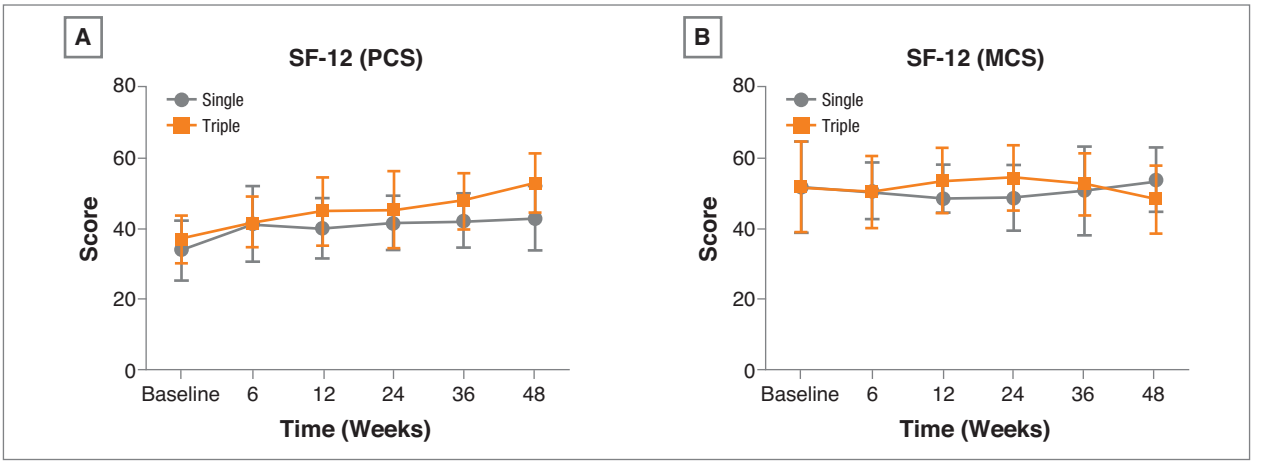

FIGURE 3. Mean (±SD) values of the scores of the physical component summary (PCS; A) and mental component summary (MCS; B) in the single and triple PRP application group. A) The PCS score increased significantly after 24 weeks in the single application (baseline 33.8 ± 8.4, 24 weeks 41.6 ± 7.6, 48 weeks 42.8 ± 9.0, p <0.05) and after 12 weeks in the triple application group (baseline 37.0 ± 6.8, 12 weeks 45.1 ± 9.7, 48 weeks 52.9 ± 8.7, p <0.05). The PCS score was higher in the triple application group at 48 weeks compared to the single application (p = 0.0124). B) There were no significant changes in the MCS score between study groups

zation, antibiotic treatment, surgical procedure, or any event not related to the treated condition that caused any contraindication for follow-up).

DISCUSSION

The most important result of this study was that the triple intraarticular injection of PRP obtained better overall clinical results in the group of patients evaluated. Although both the single and the triple application significantly decreased the level of pain and improved the functionality of the knee. The values of the VAS, Total WOMAC and the SF-12 PCS in the group of the triple application were significantly better. The clinical use of PRP as an alternative for the treatment of pathologies associated with the musculoskeletal system in orthopedics has become more frequent, especially in the treatment of knee OA. Some of the main advantages of this type of platelet concentrate are: its low cost, its preparation through a centrifugation process and the fact that it is obtained from the patient own blood.

On average, the injected PRP preparations in both groups presented a 200% increase in the number of platelets compared to that observed in whole blood. In addition, a very low number of leukocytes was quantified in the PRP preparations, less than 10% of the number of leukocytes reported in whole blood. Previously, Filardo *et al*. 2012[16], reported the use of PRP to treat joint pathologies of the knee. They showed that a similar concentration of platelets to that reported in the present study (150% more than in whole blood) produced comparable results with higher concentrations of platelets (up to 450% more than in whole blood). This result indicates that, at least clinically, a greater number of platelets will not necessarily produce better results.

The treated patients did not show major adverse events, the only recorded event was pain at the site of the injection, with a duration of no more than three days and spontaneous resolution. Like other reports, the results of the present study indicate that PRP therapy is effective and safe in the short and medium term[17,18]. On the other hand, it has been reported that patients with a lower degree of OA respond better to treatment with PRP[19,20]. This is one of the reasons why patients with mild OA were selected for this study. In addition, the results of randomized controlled studies report a higher percentage of patients who responded positively to PRP than those who did with hyaluronic acid, with a better clinical result achieved in all cases in the PRP group at a minimum follow-up of 24 weeks[21,22].

Mostly, the therapeutic protocols for the application of PRP in knee OA are divided into a single and triple application[18,22,23]. In these studies, the minimum follow-up reported was 24 weeks, in which a short to medium term response to treatment can be evaluated. In the present study, the results are shown with a 48 weeks follow-up, which allows to evaluate the clinical result in a longer time. Although several investigations have been published in recent years regarding the therapeutic use of PRP in knee OA, it is still not clear what therapeutic regimen should be followed. Some aspects have become more relevant as randomized controlled trials have been published regarding treatment with PRP. In patients with mild knee OA, PRP has shown greater clinical efficacy than hyaluronic acid; moreover, it is more effective in improving and decreasing symptoms compared to advanced OA and is more effective in younger patients and in patients with lower BMI[23–25].

An important limitation of this work is that, due to its pilot study characteristic, the study population is small; consequently, the size of the effect of the treatments in the population is not entirely reliable. However, as a consequence of conducting the study, it was possible to determine the feasibility of carrying out a larger-scale clinical study in order to test the hypothesis initially proposed.

Based on the results obtained regarding the EVA, the WOMAC index and the SF-12 questionnaire, the best results were obtained with the triple application of PRP in mild knee OA. However, the physician's decision regarding the amount and frequency of injections should be based on factors such as level of pain, physical activity, BMI, and cost-benefit in each patient. We speculated that repeating the treatment after 6 months could alleviate the symptoms for a longer period and could delay the progression of OA.

CONCLUSIONS

The therapy with the triple injection scheme of PRP in patients with mild knee OA was clinically more effective than the single application at 48 weeks of follow-up. The group of patients in the triple application showed a greater decrease in the level of pain, better

functionality of the knee and better physical performance, with a clear improvement in their quality of life. It would be important to study the clinical effect of both types of treatment in a larger patient population to corroborate these results.

CORRESPONDENCE TO
Mario Simental-Mendía
Ave. Francisco I. Madero and Dr. Eduardo Aguirre Pequeño
Tele: 528 183 294 174
E-mail: mario.simentalme@uanl.edu.mx

REFERENCES

1. Martel-Pelletier J, Boileau C, Pelletier J-P, Roughley PJ. Cartilage in normal and osteoarthritis conditions. Best Pract Res Clin Rheumatol. 2008;22(2):351–384.
2. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. World Health Organization; 2003;81(9):646–656.
3. National Clinical Guideline Centre (UK). Osteoarthritis: Care and Management in Adults. NICE Clinical Guidelines, No. 177. London: National Institute for Health and Care Excellence (UK); 2014;137-149.
4. Peláez-Ballestas I, Sanin LH, Moreno-Montoya J, Alvarez-Nemegyei J, Burgos-Vargas R, Garza-Elizondo M, et al. Epidemiology of the rheumatic diseases in Mexico. A study of 5 regions based on the COPCORD methodology. J Rheumatol. 2011;38 (86):3–6.
5. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum. 2014;43(6):701–712.
6. David C and Everts P. Platelet Rich Plasma (PRP) Matrix Graft. Pract Pain Manag. 2008;8:12–26.
7. Blunk T, Sieminski AL, Gooch KJ, Courter DL, Hollander AP, Nahir AM, et al. Differential effects of growth factors on tissue-engineered cartilage. Tissue Eng. 2002;8(1):73–84.
8. Trippel SB. Growth factors as therapeutic agents. Instr Course Lect. 1997;46:473–476.
9. Sánchez M, Anitua E, Orive G, Mujika I, Andia I. Platelet-rich therapies in the treatment of orthopaedic sport injuries. Sports Medicine. 2009;39:345–354.
10. van Buul GM, Koevoet WLM, Kops N, Bos PK, Verhaar JAN, Weinans H, et al. Platelet-Rich Plasma Releasate Inhibits Inflammatory Processes in Osteoarthritic Chondrocytes. Am J Sports Med. 2011;39(11):2362–2370.
11. Sundman EA, Cole BJ, Karas V, Della Valle C, Tetreault MW, Mohammed HO, et al. The Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis. Am J Sports Med. 2014;42(1):35–41.
12. Sánchez M, Anitua E, Azofra J, Aguirre JJ, Andia I. intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. Clin Exp Rheumatol. 26(5):910–913.
13. Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of Platelet-Rich Plasma in Patients with Primary and Secondary Knee Osteoarthritis. Am J Phys Med Rehabil. 2010;89(12):961–969.
14. 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.
15. Kijowski R, Blankenbaker D, Stanton P, Fine J, De Smet A. Arthroscopic validation of radiographic grading scales of osteoarthritis of the tibiofemoral joint. American Journal of Roentgenology. 2006;187:794–799.
16. Filardo G, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: Single- versus double-spinning approach. Knee Surgery, Sport Traumatol Arthrosc. 2012;20(10):2082–2091.
17. Jang SJ, Kim J Do, Cha SS. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. Eur J Orthop Surg Traumatol. 2013;23(5):573–580.
18. Raeissadat SA, Rayegani SM, Hassanabadi H, Fathi M, Ghorbani E, Babaee M, 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.
19. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. J Arthrosc Relat Surg. 2011;27(11):1490–1501.
20. Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. Am J Phys Med Rehabil. 2010;89(12):961–969.
21. Anitua E, Prado R, Sánchez M, Orive G. Platelet-Rich Plasma: Preparation and Formulation. Oper Tech Orthop. 2012;22 (1):25–32.
22. Vaquerizo V, Plasencia MA, Arribas I, Seijas R, Padilla S, Orive G, 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. J Arthrosc Relat Surg. 2013;29(10):1635–1643.
23. Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk 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 Surgery, Sport Traumatol Arthrosc. 2017;25(3):958–965.
24. Sánchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, Garcia Gutierrez A, 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. J Arthrosc Relat Surg. 2012;28(8):1070–1078.
25. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment With Platelet- Rich Plasma Is More Effective Than Placebo for Knee Osteoarthritis. Am J Sports Med. 2013;41:356–364.