Arch Orthop Trauma Surg (2016) 136:1723–1732
DOI 10.1007/s00402-016-2545-2

ARTHROSCOPY AND SPORTS MEDICINE

Leukocyte-poor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis

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Received: 29 February 2016 / Published online: 9 August 2016

Abstract
Introduction Knee osteoarthritis (OA) is a degenerative and progressive articular cartilage disease. Infiltration of autologous platelet-rich plasma (PRP) has been proposed as a therapeutic alternative due to the content of biologically active cytokines in PRP. We aimed to compare the clinical response of acetaminophen and intra-articular leukocyte-poor PRP (LP-PRP) in early knee OA.
Materials and methods A total of 65 patients with clinically and radiographically documented knee OA (grade 1–2) were analyzed. Patients were randomized into two groups: 32 were treated with acetaminophen (500 mg/8 h) over 6 weeks, and 33 received three intra-articular injections of autologous LP-PRP (once every 2 weeks). All patients were evaluated by the Visual Analogue Scale (VAS), the Western Ontario and McMaster Universities (WOMAC) score, and the SF-12 health survey at baseline and 6, 12, and 24 weeks of follow-up. All LP-PRP preparations were analyzed for the platelet, leukocyte, IL-1ra, and TGF-β concentrations.
Results The decrease in the VAS pain level in the LP-PRP group was greater than that in the acetaminophen group ($p < 0.05$). Patients treated with LP-PRP showed a sustained improvement in knee function at week 24 ($p < 0.01$). The SF-12 results only indicated an improvement in quality-of-life in the LP-PRP group at 6, 12, and 24 weeks of follow-up ($p < 0.01$). Both IL-1ra and TGF-β were detected in the LP-PRP samples (313.8 ± 231.6 and 21,183.8 ± 8556.3 pg/mL, respectively).
Conclusions Treatment with LP-PRP injections resulted in a significantly better clinical outcome than did treatment with acetaminophen, with sustained lower EVA and WOMAC scores and improvement in quality-of-life (higher SF-12 score). Therapy with LP-PRP may positively modify the inflammatory joint environment by counteracting IL-1β action.

Keywords Leukocyte-poor platelet-rich plasma · Acetaminophen · Osteoarthritis · Intra-articular infiltration

Introduction

Osteoarthritis (OA) is the most common cause of joint pain and has significant negative effects on the quality-of-life (QOL) of patients, particularly elderly patients due to their disabilities [1]. Currently, the non-surgical treatment for knee OA is focused on managing symptoms, such as pain and swelling, minimizing functional impairment, and preserving QOL. For patients with knee OA, the initial pharmacological treatment is mainly based in the use of acetaminophen, oral non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs, and intra-articular corticosteroids [2, 3]. Among the aforementioned pharmacological options, the rate of adverse events is higher with oral NSAIDs than with acetaminophen [4, 5]. Thus, the potential toxicity and adverse effects must be considered, because these factors limit the drug's use [6, 7].

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Common symptoms of primary knee OA are pain, swelling, and inflammation. Interleukin-1β (IL-1β) is known as a major promoter of inflammation in OA and plays a significant role in the degradation of cartilage by inducing chondrocytes and synovial cells to synthesize matrix metalloproteases. Chondrocyte synthesis pathways become ineffective as a consequence of the actions of pro-inflammatory cytokines [8]. Moreover, in the OA synovial environment, a relative deficit in the production of the IL-1 receptor antagonist (IL-1ra), which is the natural inhibitor of IL-1β, has been demonstrated. These changes lead to an imbalance in cartilage metabolism, producing extracellular matrix degradation [9].

Platelet-rich plasma (PRP) has been proposed as an alternative agent for the management of pain in knee OA [10]. PRP is a volume of plasma with a platelet concentration above the baseline value, and it is obtained from the patient's own blood [11]. The autologous nature of PRP is one of its main advantages, because this avoids any immune reaction or blood transmission disease. The number of clinical reports supporting the use of this therapy in patients with knee OA has been increasing in the last few years. However, there is limited evidence of the clinical benefits of using PRP for the treatment of symptomatic OA of the knee [12]. The existing evidence was mainly obtained by case series studies, and there is a little evidence from randomized clinical trials with control groups [12]. In the randomized trials that have been performed to date, the patient population was very heterogeneous, with patients in different stages of the disease [12, 13]; therefore, it is difficult to conclude whether this approach can be applied to a specific phase of cartilage degeneration.

PRP has been shown to be capable of reducing the IL-1β-induced inflammatory response in chondrocytes [14–16], and IL-1ra can be found in the plasma of OA patients [17]. In addition, growth factors that are present in platelets, specifically transforming growth factor-β (TGF-β), stimulate chondrocyte synthetic activity and decrease the catabolic activity of IL-1β [18]. This leads us to believe that therapy with PRP injections could reduce pain and inflammation by inhibiting the inflammatory effects of IL-1β. We used leukocyte-poor PRP (LP-PRP) to minimize the presence of inflammatory cytokines and cause a major accumulation of anabolic molecules, such as growth factors, including TGF-β.

The goals of this study were to compare LP-PRP intra-articular injections with acetaminophen in the management of symptomatic mild knee OA and to correlate the general clinical outcome in patients treated with PRP to the presence of IL-1ra and TGF-β in LP-PRP preparations.

Materials and methods

Patients and study design

This was a randomized prospective study. All patients were diagnosed with degenerative OA based on a detailed clinical history of knee pain, a complete physical examination and radiologic findings. The following inclusion criteria for patient selection were used: male or female of >18 years of age; pain, inflammation, or any other symptom related to knee OA lasting at least 3 months; no use of NSAIDs; and radiologic signs of grade 1 or 2 knee OA according to the Kellgren–Lawrence classification system [19]. The exclusion criteria were as follows: any surgical intervention of the knee, pregnancy, rheumatic disease, hepatological disease, liver disease, severe cardiovascular disease, diabetes, coagulopathy, infection, immunodepression, anticoagulant therapy, and an Hb value <11 g/dL and platelet value <150,000/μL (Fig. 1). In patients with bilateral OA, only the knee that reflected more significant symptoms was considered.

Platelet-rich plasma preparation

A 27-mL venous blood sample in 6 vacutainer tubes with 0.109-M sodium citrate was used for each injection (369714, BD Vacutainer, Franklin Lakes, NJ, USA). Samples were gently agitated to ensure mixing of the anticoagulant with the blood. An extra tube with anticoagulated EDTA blood was obtained for the initial platelet count (368171, BD Vacutainer, Franklin Lakes, NJ, USA). Blood samples were centrifuged for 10 min at 1800 rpm to separate the erythrocyte layer. The upper plasma layer was carefully collected in a new sterile propylene tube while attempting to not remove the leukocyte layer. The plasma from all tubes was centrifuged again for 12 min at 3400 rpm to obtain a two-part plasma, with the upper part consisting of platelet-poor plasma and the lower part consisting of LP-PRP. The platelet-poor plasma was discarded to obtain a final volume of 3 mL. This volume of LP-PRP was mixed carefully by pipetting to resuspend the platelets, and it was then transferred to a new sterile glass tube. An aliquot of the final LP-PRP was sent to the laboratory for a platelet count. All open handling sample procedures were performed within a high-efficiency particulate air-filtered laminar flow hood (Logic A2, Labconco, Fort Scott, KS, USA).

Treatment procedure

Patients were divided into two groups in a randomized fashion. One group was treated with acetaminophen at a

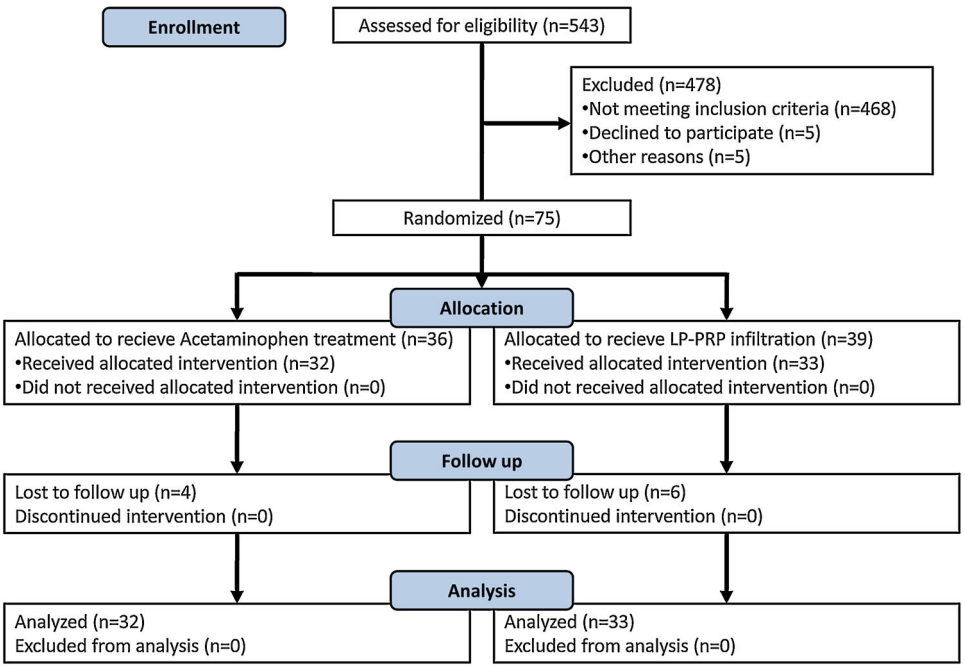

Fig. 1 Flow diagram of the study. *n* number of patients, *LP-PRP* leukocyte-poor platelet-rich plasma

dosage of 500 mg every 8 h for 6 weeks. No other medication was allowed during treatment. The other group was treated using intra-articular injections of autologous LP-PRP. A total of three injections were performed over 6 weeks, with one injection every 2 weeks. The injections were administered after disinfection of the skin in the knee joint area with Avagard D (3 M Health Care, St. Paul, MN, USA). After local anesthesia with lidocaine chlorohydrate (Laboratorios PISA, Guadalajara, México), the platelets were activated using 10 % calcium gluconate solution (Laboratorios PISA, Guadalajara, México), and the liquid LP-PRP was injected under a sterile condition using a 22-G needle. The needle was inserted using the inferolateral approach at an angle of approximately 45°.

Quantification of IL-1ra and TGF-β

An aliquot of each activated LP-PRP (aPRP) was centrifuged once a clot formed; the aPRP was then recovered and stored at −80 °C until analysis. The IL-1ra and TGF-β levels were measured using a commercially available ELISA kit (Quantikine®, DRA00B and DB100B, R&D Systems Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. All three PRP samples from each patient were analyzed.

Post-procedure management and follow-up

Patients from the LP-PRP group were asked to flex and extend their knees immediately after injection, so that the LP-PRP could distribute adequately across the joint space. After 10 min of observation, the patients were sent home with written instructions, including relative rest for 24–48 h after the injection, the use of cold therapy for 15 min three times a day, and the use of 500 mg of acetaminophen if pain and inflammation develop. The use of NSAIDs or any steroids was prohibited. All patients were evaluated before the beginning of their treatments and at 6, 12, and 24 weeks after their treatments. Three different scales were used to evaluate clinical outcome: the Visual Analogue Scale (VAS), which scores pain level [20]; the Western Ontario and McMaster Universities Arthritis Index (WOMAC), which assesses pain, articular stiffness, and functional limitation [21]; and the Spanish (México) version of the Short Form-12 (SF-12), which assesses QOL [22].

Statistical analysis

The non-parametric Chi-square test and Fisher's exact test were used to investigate differences between the two groups. All continuous data are expressed as the means and the standard deviation of the mean. One-way ANOVA with Tukey's multiple comparison post-hoc test was performed to assess differences between groups. The data were analyzed and graphic were created using the software GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA). For all tests, $p < 0.05$ was considered significant. The sample size calculations indicated that a sample size of 28 patients per group would result in 95 % power given a standard deviation of 20 points in the WOMAC score and an alpha level of 0.05, with a

minimum clinically significant difference of 15 points based on existing data [23]. We included 15 % more patients than the number determined by the sample size calculation in anticipation of losing some patients to follow-up.

Compliance with ethical standards

The clinical experiments were approved by the University Hospital and Faculty of Medicine Ethics Committee and the Internal Review Board, Autonomous University of Nuevo León (BI13-001), and informed consent was obtained from all patients. The study was registered in the public trial registry clinicaltrials.gov (identifier NCT01782885) and conducted in accordance with the Helsinki Declaration.

Results

A total of 75 patients with primary knee OA were enrolled in this study. Ten patients were not included, because they were lost to follow-up. Sixty-five patients were included in the analysis (23 men and 42 women). Twenty-three patients presented with grade 1 knee OA, and 42 presented with grade 2 knee OA. The acetaminophen group consisted of 32 patients, and the LP-PRP group consisted of 33 patients. Patient age was not significantly different between the two groups ($p > 0.05$). A higher percentage of women than men was present in both groups (acetaminophen group: 62 % women, LP-PRP group: 67 % women), and the percentage of women was not significantly different between the groups ($p > 0.05$). The mean BMI was not statistically significantly different between the groups (acetaminophen group: 29.5 ± 3.8 vs LP-PRP group: 32.2 ± 6.2; $p > 0.05$). Patient demographic information is reported in Table 1. The mean VAS score at baseline for the acetaminophen group was 5.9 ± 2.2, and that for the PRP group was 4.9 ± 2.4 ($p > 0.05$). The baseline total WOMAC score was 35.5 ± 19 for the acetaminophen group and 35.7 ± 19.5 for the LP-PRP group ($p > 0.05$).

The mean platelet count in whole blood was 251.06 ± 69.1 K/μL, and that in LP-PRP was 513.25 ± 189.3 K/μL. On average, the mean platelet concentration was 2.04 times greater in LP-PRP than in whole blood. On average, the numbers of leukocytes were 6.89 ± 2.19 K/μL and 0.52 ± 0.46 in whole blood and LP-PRP, respectively. The mean leukocyte count was 13.3 times lower in LP-PRP than in whole blood (Table 2). The levels of IL-1ra and TGF-β were detectable in all aPRP samples and the coefficient of variation (CV) values for the IL-1ra and TGF-β levels among the three interventions were 6.71 and 8.34 %, respectively (Table 2).

The VAS score for pain was significantly lower in both groups at all follow-up time points in comparison with baseline (Fig. 2). However, the diminution in pain level was greater in the LP-PRP group than in the acetaminophen group (LP-PRP group: $p < 0.001$ vs acetaminophen group: $p < 0.01$). The most significant difference between the groups was shown at week 12: the VAS score for the LP-PRP group was 1.9 ± 1.6, whereas that for the acetaminophen group was 4.1 ± 2.6 ($p < 0.01$).

Scores for stiffness, pain, and functional capacity were lower at all follow-up time points in both groups in comparison to baseline (Fig. 3); however, these decreases from the baseline scores were only significant in the LP-PRP group ($p < 0.001$). The comparison of all three items between the groups showed a significant difference for pain and functional capacity in favor of the LP-PRP treatment. Significant differences in pain between the groups were noted at 6 and 12 weeks of follow-up ($p < 0.05$), with

Table 1 Two treatment groups are homogeneous for all the parameters evaluated

	Comparative demographics		
	Acetaminophen	LP-PRP	*p* value
Patients	32	33	
Age	55.6 ± 11.4	57.2 ± 8.1	0.567
Sex	62 % F, 38 % M	67 % F, 33 % M	1.0
BMI	29.5 ± 3.8	32.2 ± 6.2	0.336
Kellgren–Lawrence			
Grade 1	12 (37 %)	11 (33 %)	0.802
Grade 2	20 (63 %)	22 (67 %)	0.943
Baseline VAS	5.9 ± 2.2	4.9 ± 2.4	0.111
Baseline WOMAC	35.5 ± 19	35.7 ± 19.5	0.798

LP-PRP leukocyte-poor platelet-rich plasma, *BMI* body mass index, *VAS* Visual Analogue Scale, *WOMAC* Western Ontario and McMaster Universities Arthritis Index

Table 2 Analyses of blood components, LP-PRP, and activated LP-PRP from patients in the LP-PRP group

Blood component	Blood component analyses			Evaluated cytokine	aPRP analyses			CV (%)
	Average concentration (K/μL)				Average concentration (pg/mL)			
	Whole blood	LP-PRP	*N*-fold change		LP-PRP 1	LP-PRP 2	LP-PRP 3	
Platelets	251.06 ± 69.1	513.25 ± 189.3	2.04	IL-1ra	274.3 ± 124	293.4 ± 167.1	313.8 ± 231.6	6.71
Leukocytes	6.89 ± 2.19	0.52 ± 0.46	13.25	TGF-β	20435 ± 5287	19461 ± 4231	21183 ± 8556	8.34

LP-PRP leukocyte-poor platelet-rich plasma, *aPRP* activated LP-PRP, *IL-1ra* interleukin-1 receptor antagonist, *TGF-β* transforming growth factor-β, *CV* coefficient of variation

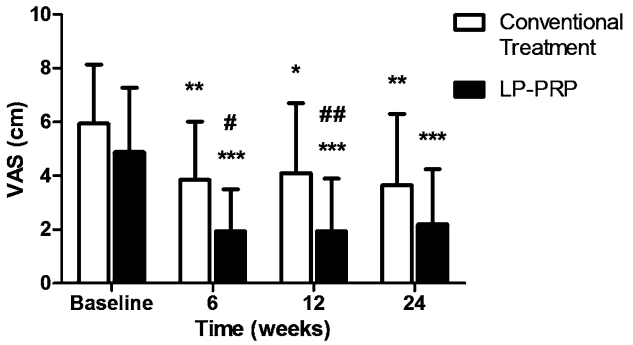

Fig. 2 Mean value of VAS in the conventional treatment group and the LP-PRP group. The LP-PRP group had significantly lower VAS scores at all-time points of evaluation ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs baseline values; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs conventional treatment group)

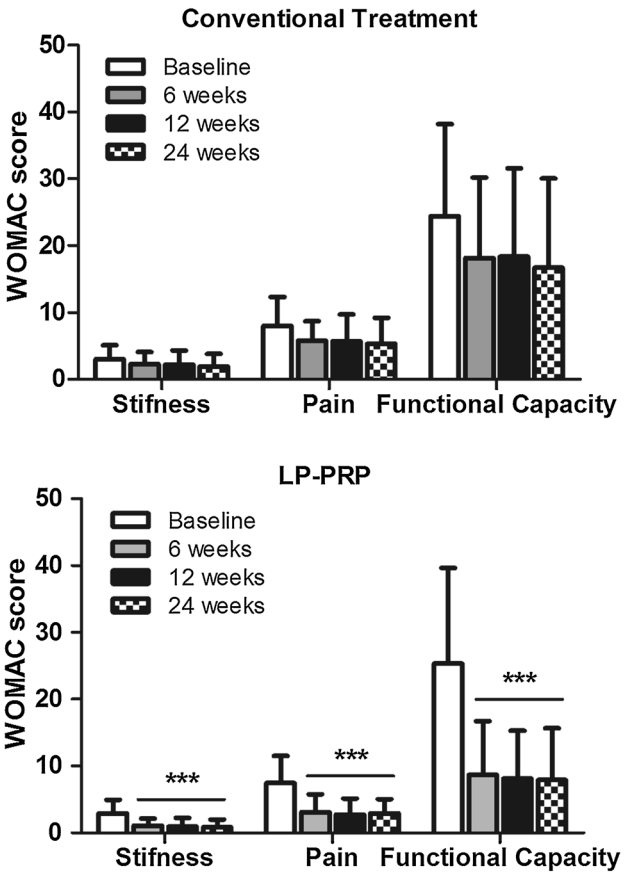

Fig. 3 Mean WOMAC subcategories scores for the conventional treatment group and the LP-PRP group. The scores were lower at all follow-up time points in both groups in comparison with baseline. These decreases from the baseline scores were only significant in the LP-PRP group ($^{***}p < 0.001$ vs baseline)

scores of 5.8 ± 2.9 and 5.7 ± 3.9 in the acetaminophen group and scores of 3.1 ± 2.6 and 2.7 ± 2.4 in the LP-PRP group. Functional capacity was significantly different between the groups at 6, 12, and 24 weeks of follow-up ($p < 0.05$), with scores of 18.2 ± 12.0, 18.3 ± 12.7, and 16.7 ± 13.3 in the acetaminophen group and scores of 8.7 ± 8.0, 8.3 ± 7.3, and 7.9 ± 7.7 in the LP-PRP group, respectively.

Both groups showed a significant reduction in the overall WOMAC score compared with baseline at all follow-up time points ($p < 0.05$ for the acetaminophen group and $p < 0.001$ for the LP-PRP group). At all follow-up time points, the difference in the overall WOMAC score between the two groups was statistically significant ($p < 0.05$). The mean WOMAC scores at 6, 12, and 24 weeks were 26.2 ± 16.0, 26.3 ± 17.8, and 24.0 ± 18.6 in the acetaminophen group and 12.8 ± 11.0, 12.0 ± 10.6, and 11.7 ± 10.0 in the LP-PRP group, respectively (Fig. 4).

For the SF-12, the mean changes in the two major physical and mental domains were only significant in the LP-PRP group ($p < 0.001$). The mean mental component summary (MCS) at baseline and 6, 12, and 24 weeks of follow-up were 44.2 ± 11.8, 55.4 ± 8.7, 55.9 ± 7.9, and 54.3 ± 7.6, respectively (Fig. 5). The mean physical component summary (PCS) at baseline and 6, 12, and 24 weeks of follow-up were 38.0 ± 8.0, 47.6 ± 7.9, 48.8 ± 7.9, and 49.9 ± 8.1, respectively. In the LP-PRP group, all components of the QOL score (Fig. 6), except for the general health variable, had improved at the 24-week follow-up evaluation compared with their baseline values (at least $p < 0.05$).

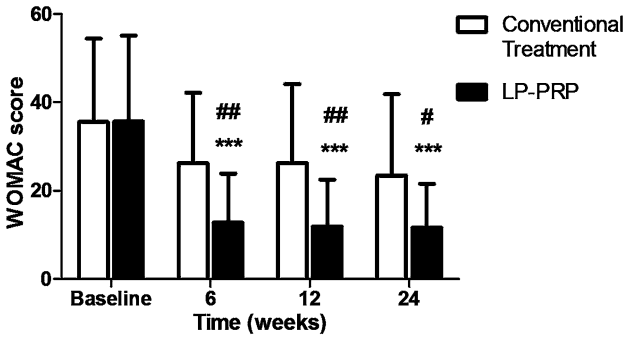

Fig. 4 Mean total WOMAC score in the conventional treatment group and the LP-PRP group. Both groups showed a significant reduction in the overall WOMAC score compared with baseline. The difference in the overall WOMAC score between the two groups was statistically significant (***$p < 0.001$ vs baseline; $^{\#}p < 0.01$, $^{\#\#}p < 0.01$ vs conventional treatment group)

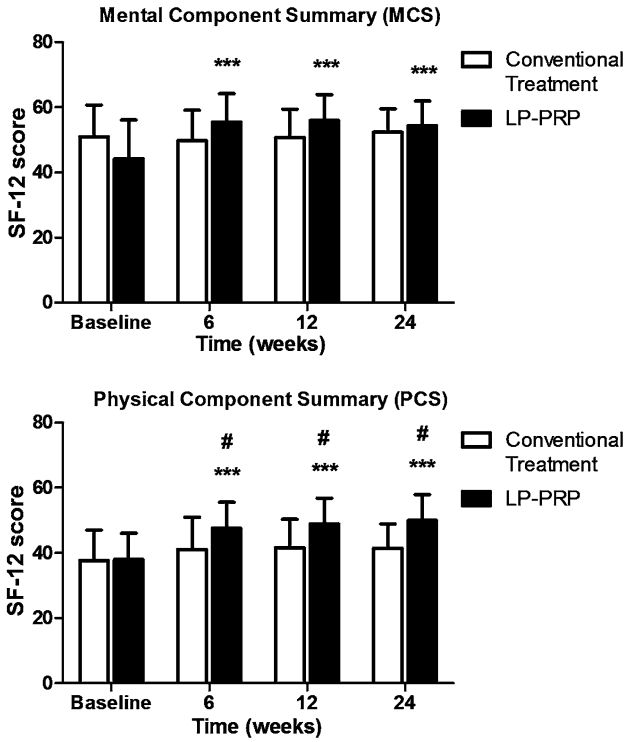

Fig. 5 Mean SF-12 PCS and MCS scores in the conventional treatment group and the LP-PRP group. Only the LP-PRP group showed a significant improvement in the two major physical and mental domains (***$p < 0.01$ vs baseline; $^{\#}p < 0.05$ vs conventional treatment group)

Discussion

The clinical use of PRP is becoming more frequent in the treatment of symptomatic knee OA. The main advantages of platelet concentrates are their low cost, their preparation through a simple centrifugation process, and the fact that they are obtained from the patient's own blood. A wide range of PRP formulations exists as a result of the lack of optimization and standardization of PRP preparations with different potential biological applications [24, 25].

In this study, we used an LP-PRP, because it has been noted that the presence of white blood cells in the space joint could generate a negative pro-inflammatory environment in OA cartilage. Although some of these changes are transient, they include an increase in inflammatory IL-1 activity, activation of NF-κB and COX-2 expression, and promotion of catabolic pathways [15, 26]. In addition, more swelling and pain reactions have been reported when using leukocyte-rich PRP (LR-PRP) [27]. Despite these reports, it is still unclear whether leukocytes in PRP have an adverse effect.

On average, our LP-PRP preparations had twice as many platelets as did whole blood and a very low number of leukocytes (less than 10 % of the amount of leukocytes in whole blood). A previous report by Filardo et al. [27], who used PRP to treat degenerative articular pathology of the knee, showed that a similar concentration of platelets to that used here (1.5-fold greater than in whole blood) produced comparable results to higher concentrations of platelets (4.5-fold greater than in whole blood). This result indicates that a higher amount of platelets would not necessarily produce a better clinical outcome. In a recent meta-analysis, it was concluded that LP-PRP results in improved functional outcome scores compared with hyaluronic acid and placebo when used for the treatment of knee OA [28]. However, other researchers have mentioned that there is limited evidence for comparing the clinical outcomes of LR-PRP versus LP-PRP [29]. Further randomized trials are needed to further assess and to compare the efficacy of LR-PRP and LP-PRP.

Similar to other investigations, our study indicated the efficacy and safety of PRP therapy in the short-term [8, 30, 31]. The treated patients reported no major adverse events; the only adverse event recorded was mild pain in the infiltration site that lasted no more than 3 days with spontaneous resolution. It has been reported that younger patients with a lower grade of OA respond better to treatment with PRP [32, 33]. Though our patients had an average age of over 50 years, the patients in the LP-PRP group showed sustained improvement through the follow-up period, without symptoms and without the use of any other medication. This is consistent with the results of recent controlled randomized studies, where the efficacy of PRP treatment was compared with that of hyaluronic acid. Those studies reported that a higher percentage of patients positively responded to PRP than to hyaluronic acid, with a better clinical outcome achieved in all the cases in the PRP group at a minimum of 24 weeks of follow-up [34–36]. Recent analyses of clinical evidence have concluded that intra-articular injections of PRP in patients with symptomatic knee OA result in a significantly reduced level of

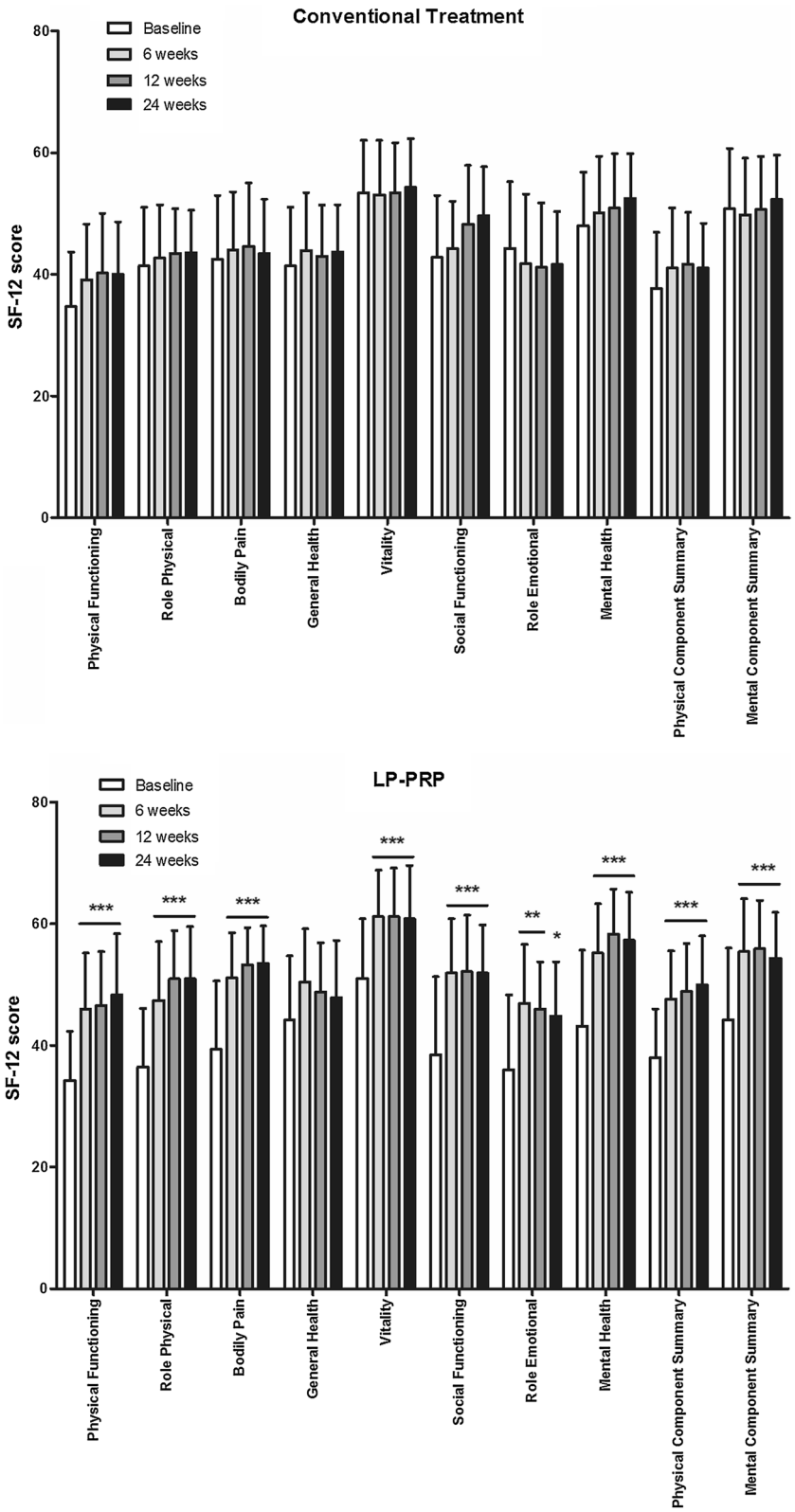

Fig. 6 Mean SF-12 components scores in the conventional treatment group and the LP-PRP group. All components of the score (except for the general health variable) improved at the 24-week follow-up evaluation compared with their baseline values in the LP-PRP group (*$p < 0.05$, **$p < 0.01$, ***$p < 0.01$ vs baseline values)

pain, improved functional outcomes, and improved QOL when compared with hyaluronic acid and placebo [29, 37, 38], supporting the results of this study.

In the previous investigations, patients treated with PRP had variable grades of OA (from I to IV according to the Kellgren–Lawrence classification system), which resulted

in high variability in response to treatment: the higher the grade of OA was, the lower the response to treatment was [27, 30, 32, 39]. Only patients with OA grade 1 or 2 were included in our study to form a homogeneous patient population. The treatment for these patients is essentially pharmacological; the acetaminophen has been for decades considered as a core treatment for knee OA in the first recommendations from consensus guidelines, because of its efficacy and good safety profile [3, 40]. Nevertheless, a recent update of the evidence led to investigators from organizations, such as the Osteoarthritis Research Society International (OARSI) and the American Academy of Orthopaedic Surgeons (AAOS), to infer that evidence for the efficacy of use of acetaminophen in the pharmacological management of knee pain in OA has diminished [6, 41]. Although there have been reports indicating that acetaminophen did not have an expected symptomatic effect over placebo [42], a more recent meta-analysis confirms the efficacy of acetaminophen over placebo, albeit at a low level in patients with OA [40]. It has also been stated that acetaminophen may still have utility as a short-term analgesic in OA, as it was evaluated in this study [6, 40]. In accordance with our study, other authors have concluded that acetaminophen should be used at the lowest effective dosage and for the shortest time in patients with OA; and that given the different safety profiles, the choice of NSAIDs, should be based on individual patient risk factors [43]. For these reasons, we chose to compare LP-PRP with acetaminophen. In addition, 94 % of patients treated with LP-PRP responded favorably and demonstrated a reduction in the total WOMAC score in our study population.

PRP has also received attention as an alternative treatment for cartilage regeneration based on the results of investigations focusing on its use. In vitro studies have reported that PRP is capable of inhibiting the inflammatory process in OA chondrocytes [14] and that it has the potential to prevent the loss or degradation of cartilage associated with the degenerative process of OA [44]. This finding suggests that the combination of anabolic and anti-inflammatory molecules present in PRP makes it an ideal candidate for the treatment of OA.

In our study, we were able to detect IL-1ra and TGF-β in all LP-PRP samples after each of the three injections in all patients. An IL-1ra concentration of 10–1000 times higher than that of IL-1β is necessary to counteract the pro-inflammatory effect of IL-1β [13, 45]. On average, the levels of IL-1ra detected in our LP-PRP samples (274.3 ± 124, 293 ± 167.1, and 313.8 ± 231.6 pg/mL) could be sufficiently high to inhibit the activity of IL-1β, according to the previously reported concentration of IL-1β in the synovial fluid of patients with knee OA (7.6–27.8 pg/mL) [13, 46]. PRP is also known to stimulate cell proliferation and matrix production. This is due to the presence of growth factors in PRP that regulates the expression of the chondrocyte phenotype, which plays a major role in OA progression. In particular, TGF-β has the capacity of decrease the catabolic activity of IL-1β by stimulating the synthesis of extracellular matrix proteins (proteoglycans, type II collagen) [18]. Based on the levels of TGF-β found in our LP-PRP samples (20.4 ± 5.3, 19.5 ± 4.2, and 21.2 ± 8.6 ng/mL) and the concentrations of this growth factor used previously in in vitro assays (0.3 ± 20.0 ng/mL), our LP-PRP samples should have possessed chondrogenic activity [47, 48].

Conclusions

Treatment with PRP infiltration was more efficient than the conventional pharmacological therapy in patients with mild knee OA in terms of the reduction of knee pain, increase in knee functionality, and significant improvement of QOL. Therapy with PRP can favorably modify the articular inflammatory environment and the progression of OA due to the presence of therapeutic concentrations of IL-1ra and TGF-β in LP-PRP. Intra-articular infiltrations with LP-PRP could prevent further degeneration of cartilage by retarding OA progression in the first stages of the disease.

Acknowledgments M. Simental-Mendía received a fellowship from the Consejo Nacional de Ciencia y Tecnología (CONACYT), México.

Compliance with ethical standards

Conflict of interest None.

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