THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Original Research

Real-world evidence to assess the effectiveness of platelet-rich plasma in the treatment of knee degenerative pathology: a prospective observational study

Ther Adv Musculoskel Dis

2022, Vol. 14: 1–14

DOI: 10.1177/1759720X221100304

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Abstract

Objective: The present work aims to analyse the effectiveness of platelet-rich plasma (PRP) in degenerative knee pathology based on real-world data and to evaluate possible factors influencing the response to treatment.

Methods: In total, 531 cases were analysed collecting data on gender, age, body mass index, pathology location, severity, number of cycles and route of administration. Clinical outcome was evaluated at 6 and 15 months after treatment, using the Knee injury and Osteoarthritis Outcome Score (KOOS) and obtaining percentages of Minimal Clinically Important Improvement (MCII). Blood and PRP samples were randomly tested as a quality control measure to ensure the correct properties. Comparative statistical tests and multivariate regression were performed for the analysis of the variables.

Results: The PRP applied had a platelet concentration factor of 1.67, with no leukocytes or erythrocytes. The percentage of patients with MCII at 6 and 15 months after PRP application was 59.32% and 70.62%, respectively. Patients with MCII were younger ($p = 0.0246$) and with lower body mass index ($p = 0.0450$). The treatment had a better response in mild/moderate cases than in severe cases ($p = 0.0002$). Intraosseous PRP application in severe cases improved the effect of intraarticular PRP ($p = 0.0358$). The application of a second cycle of PRP only improved the response in patients without MCII at 6 months ($p = 0.0029$), especially in mild/moderate cases ($p = 0.0357$).

Conclusion: The applications of PRP in degenerative knee pathologies is an effective treatment, but this effectiveness nonetheless depends on several variables. Real-world data can complement that from clinical trials to provide valuable information.

Keywords: intraarticular, intraosseous, knee joint degeneration, platelet-rich plasma, real-world evidence

Received: 22 September 2021; revised manuscript accepted: 26 April 2022.

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Introduction

Knee joint degeneration is a highly disabling disease, especially in the elderly population, with a prevalence of more than 15% worldwide, and more than 40% in patients over 40 years of age.[1] Today's habits such as sedentarism, obesity and an ageing population will inevitably lead to an increase in prevalence in the coming years, not only in the elderly population but also in young patients.[2] Its complexity is another obstacle that makes it a challenge for health systems, because other structures besides the cartilage are involved, namely, the synovial membrane and the subchondral bone.[3] The lack of a clear therapeutic target and its degenerative nature make it difficult to apply effective treatment to stop or slow its

progression. Current treatments, such as oral or intraarticular pharmacology, achieve symptom relief but do not resolve this disease, making total knee arthroplasty the definitive solution for these patients. However, this surgical intervention is contraindicated in patients of advanced age or with multiple comorbidities, not to mention the inherent surgical risks and associated costs.[4,5]

Treatments based on regenerative medicine, such as platelet-rich plasma (PRP) or cell therapies, aim to expand therapeutic arsenal so as to avoid or delay surgery as far as possible. While cell therapy is still in its infancy and has to overcome several challenges, PRP has been applied for more than 15 years with a consolidated position in the treatment of this disease.[6] It is based on obtaining the plasma fraction from the patient's blood with a concentration of platelets similar to or higher than in blood levels. PRP contains high levels of biomolecules that participate in different biological processes that favouring cellular repair.[7]

An increasing number of randomized clinical trials (RCTs) are being conducted to draw firm conclusions regarding the efficacy and safety of PRP, with promising results.[8] Although RCTs are the cornerstone of evidence-based medicine, their use for the study of PRP has certain limitations. The term PRP encompasses a range of products of different compositions, which makes a proper comparison between the different studies impossible and leads to contradictory results. This also prevents the aggregation of patients from different RCTs for the analysis of large population samples. On the contrary, the information obtained from real-world evidence (RWE) studies may be a useful complement to the data obtained from RCTs. RWE can be defined as the collection of clinical data from patients in routine clinical practice. Although it does not have all the strengths of RCTs, it allows the real-world data collection from a large volume of patients and the assessment of various factors that may influence treatment.[9,10] The combination of both types of study provides the medical and scientific community with valuable information for the further study of pathologies and treatments. However, there are hardly any RWE studies on knee degeneration and PRP.[11,12]

We hypothesize that conducting RWE studies could provide information to help optimize treatment protocols. Thus, the present work aims to analyse the effectiveness of PRP in knee degenerative pathology, based on a large number of patients, and to evaluate possible factors influencing the response to treatment.

Methods

Study design, patients and data collection

The study was designed as a prospective observational study to analyse PRP application in knee degenerative pathology. This study was carried out in accordance with the International Declaration of Helsinki in Fortaleza, Brazil (2013), Good Clinical Practice Regulations and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[13] Ethical approval for this study (Protocol No. EPA2015046) was obtained from the Ethics Committee of the Basque Country (September 2015), as was written informed consent.

The eligible patients were enrolled consecutively between 2015 and 2020 in the same medical centre. They met the following inclusion criteria: patients of both sexes over 18 years old, diagnosed with knee joint degeneration and a complete follow-up for a minimum of 12 months. The exclusion criteria were as follows: associated joint pathologies or systemic autoimmune rheumatic disease, and any knee intervention or intraarticular infiltrations in the past 12 months or during PRP treatment and follow-up.

Age, sex, body mass index (BMI), number of PRP cycles (one or two), route of administration (intraarticular or intraosseous), presence of synovial fluid, location and pathological severity were collected. Imaging studies assessed pathological severity using the Ahlbäck and Outbridge scales for osteoarthritis and chondropathies, respectively. Patients were divided into two categories: mild or moderate grade (Ahlbäck: I–II; Outbridge: 1–2) and severe grade (Ahlbäck: III–IV, Outbridge 3–4). Patients completed the Knee injury and Osteoarthritis Outcome Score (KOOS) to assess their response to treatment. Concurrent medication such as paracetamol was forbidden 48 h before assessment. All data were collected through the use of electronic medical records.

PRP preparation

Depending on whether infiltration was intraarticular or intraosseous, 32 or 80 ml of venous blood was extracted from the patient, respectively. The

blood was withdrawn into 9-ml tubes containing 3.8% (w/v) sodium citrate and centrifuged at $580 \times g$ for 8 min at room temperature (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain). The 2-ml plasma fraction located above the red blood fraction, but not including the buffy coat, was collected. This plasma fraction contained a moderate concentration of platelets (1.5–2.5 times compared with peripheral blood) and an absence of erythrocytes and leukocytes. Calcium chloride (10% w/v) was added as an activator. All procedures were performed under sterile conditions.[14]

PRP quality control

During routine clinical practice, blood and PRP samples are collected randomly and periodically from patients undergoing treatment. Both types of samples are analysed in the Sysmex XS-1000i haematology analyser (Sysmex, Kobe, Japan) to verify that the PRP is elaborated correctly and complies with the parameters indicated by the manufacturer.

Treatments

The intraarticular administration consisted of 8 ml of PRP infiltrated into the articular space after evacuating the totality of the synovial fluid. One PRP cycle consisted of three intraarticular infiltrations on a weekly basis.

In the first treatment visit, intraosseous administration included three different injections of 2 ml (patella) and 5 ml (femoral head and tibial plateau) into different anatomical locations, conducted in the operating room. Following one PRP intraarticular injection, two PRP intraosseous injections were performed depending on the location of the degeneration, in accordance with the technique described by Sánchez *et al.*[15] Two more intraarticular PRP infiltrations were performed over the 2 weeks following the first visit to complete the PRP administration cycle.[16]

In both cases, patients could opt for a second PRP cycle approximately 6 months after the first, depending on the physician's recommendation after a follow-up visit which consisted of a clinical and physical evaluation.

Outcome evaluation

Patients filled out KOOS at baseline, 6 months and 15 months (a follow-up window of between 12 and 18 months) after the third injection of the first cycle of PRP. The primary efficacy criterion was a change from baseline in joint pain, measured using the KOOS pain subscale. Success rates were calculated according to a reduction in the pain score of at least 10 points from baseline (Minimal Clinically Important Improvement (MCII)).[17] Secondary variables included changes in KOOS subscales for symptoms, activities of daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL).

Statistical analyses

Demographic and medical variables were determined by the mean and standard deviation for parametric data, and median and 95% confidence interval (CI) for non-parametric data. A comparison of the patients' success rate percentages was carried out using the χ^2 test. Comparisons were performed by Student's t test for independent or paired parametric data, Wilcoxon signed-rank test for paired non-parametric data and Mann–Whitney U test for independent non-parametric data. Multivariate logistic regression was performed to analyse the influence of the different variables considered collectively, calculating coefficients (B), p value, odds ratios (ORs) and 95% CI. Distribution of the samples was assessed by Shapiro–Wilk's test. Data were considered statistically significant when $p < 0.05$. Statistical analysis was performed with SPSS 20.0 (SPSS, Chicago, IL, USA).

Results

PRP characterization

A total of 445 blood samples and corresponding PRP sample were analysed at random. The median PRP platelet concentration was 309×10^3 platelets/µl (CI: 297–327), reaching a concentration factor of 1.67 (CI: 1.63–1.73), and with no leukocytes or erythrocytes. In accordance with the latest coding system and minimum reporting requirements for PRP studies, the PRP used in this study was 13-00-11, and the characteristics of the PRP are reported in Table 1.[18]

Demographics, the overall effectiveness of PRP and influence of patient factors

The study analysed a total of 441 patients (531 knees; Figure 1). The median age was 60.47 years

Table 1. Characteristics of platelet rich-plasma.

Parameter	Values
PRP preparation	
Initial blood volume	32 ml (intraarticular) or 80 ml (intraosseous)
Anticoagulant	Sodium citrate 3.8% (w/v)
System	Close
Centrifugation	Yes
Number	1
Speed	580 × *g* for 8 min
Final PRP volume	8 ml (intraarticular) or 20 ml (intraosseous)
PRP characteristics	
PRP type	13-00-11
MPV	9.60 fl (CI: 9.50–9.80)
Red blood cells	$<0.01 \times 10^6$/µl
White blood cells	$<0.05 \times 10^6$/µl
Neutrophils	–
Lymphocytes	–
Monocytes	–
Eosinophils	–
Basophils	–
Activation	$CaCl_2$ (10% w/v)
Application characteristics	
Formulation type	Liquid
Administration route	Intraarticular or intraosseous
Dosage	3 infiltrations on a weekly basis
Volume	Intraarticular injection: 8 ml Intraosseous injection: 3–5 ml
Dose (range of platelets)	Intraarticular injection: 2.37×10^9–2.62×10^9 Intraosseous injection: 0.89×10^9–1.64×10^9
Tissue	Cartilage, synovium, subchondral bone
Pathology	Knee joint degeneration

CI, confidence interval; PRP, platelet-rich plasma; MPV, mean platelet volume.

(CI: 59.41–61.87), with a mean BMI of 28.65 (CI: 28.09–29.25) and a percentage of females of 47.47%. The percentage of cases who showed a pain reduction of at least 10 points (MCII) from baseline to 6 months was 59.32% (315 out of 531), and 70.62% (375 out of 531) by 15 months. All KOOS scores showed a significant statistical increase at 6 months post-treatment, with improvement maintained at 15 months post-treatment ($p < 0.0001$; Figure 2).

Patients with MCII at both 6 and 15 months were significantly younger than those not experiencing clinical improvement, with a median age of 62 years at 6 months (CI: 60–64) compared with 65 years (CI: 63–66) ($p = 0.0137$). At 15 months, the age of patients with MCII (62; CI: 60–63) was significantly lower than that of patients without MCII (65; CI: 64–67) ($p = 0.0246$). Concerning BMI, at 15 months, patients with MCII (27.62; CI: 27.00–28.23) presented a BMI significantly lower than that of patients without MCII (28.03; CI: 27.41–29.51) ($p = 0.0450$).

Influence of pathology factors: severity and location

Of the 531 cases, 39.36% (209 out of 531) were mild/moderate, and the response of these was 66.03% at 6 months and 79.90% at 15 months, 11.06 percentage points higher than the severe cases at 6 months (CI: 2.52–19.23; $p = 0.0113$) and 15.31 percentage points higher at 15 months (CI: 7.52–22.56; $p = 0.0002$) (Figure 3). The difference in scores for increase in pain ($p = 0.0040$) and Sport/Rec ($p = 0.0457$) between these two groups was also significant. There was no difference in age ($p = 0.3611$) or BMI ($p = 0.24.96$) between patients in the two severity groups.

Of the cases, 48% presented synovial fluid leakage in the knee (254 out of 531), this being a significant feature in severe osteoarthritis with a difference of 22.05 (CI: 14.41–30.16) percentage points compared with mild/moderate pathologies ($p < 0.0001$). The presence of synovial fluid did not influence treatment efficacy. At 6 and 15 months post-treatment, the percentage of patients with no more joint effusion was 73.62% and 68.50%, respectively.

The extension of degeneration did not influence the clinical outcomes of PRP (Supplementary Table S1). In unicompartmental pathologies, mild/moderate cases affecting the patellofemoral joint achieved a better result than tibiofemoral cases of the same grade (Supplementary Table S2). Those patients were much younger (39 years; CI: 35–45) and had a lower BMI (25.50; CI:

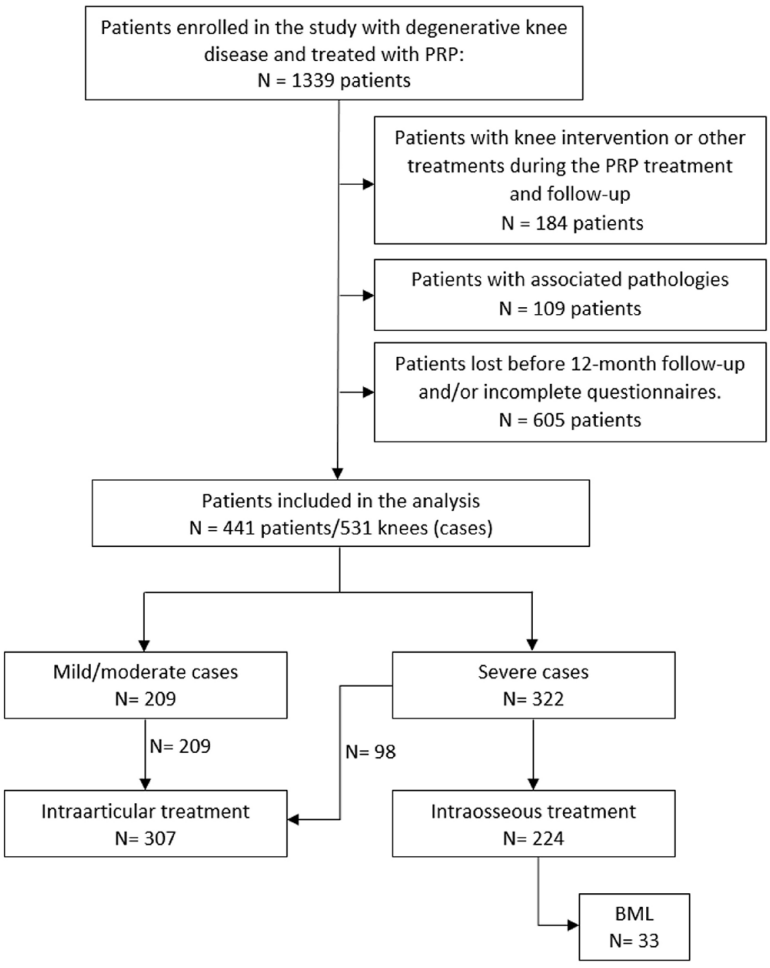

Figure 1. Study flowchart. Selection of eligible patients and distribution of cases analysed according to severity and treatment.
BML, bone marrow lesion; PRP, platelet-rich plasma.

24.02–25.90) than those with mild/moderate tibiofemoral degeneration (66 years; CI: 64–48 and 28.48; CI: 26.96–30.88). Detailed analysis of all locations showed no difference in treatment response (Supplementary Table S3).

Influence of protocol factors: PRP cycles and administration route

Of all the cases analysed, 117 opted for a second PRP cycle after the first follow-up period, 63 without MCII at 6 months and 54 with a positive response (Figure 4). Of the first 63 patients, 37 achieved MCII after the second PRP cycle (58.73%), 22.13 points higher than the group showing no MCII at 6 months and that did not receive a second cycle of PRP (CI: 7.51–35.54; $p = 0.0029$). This improvement was only observed in mild/moderate pathologies, with 25.25 percentage points more in the group with the second cycle of PRP (CI: 1.93–44.82.54; $p = 0.0357$; Supplementary Table S4). In terms of the effect of a second PRP cycle in sustaining the effect of treatment over time, there was no difference between the 54 patients with MCII at 6 months who opted for a second PRP cycle *versus* those who did not repeat the PRP cycle ($p = 0.1951$; Supplementary Table S5).

Of the 531 cases, 307 received intraarticular treatment, with 59.61% of patients (183 out of 307) showing MCII at 6 months and 72.31% at 15 months (222 out of 307). This improvement was greater in mild/moderate pathology cases, at 66.03% (138 out of 209) and 79.90% (167 out of 209), respectively. However, in severe pathologies, MCII was 45.91% (45 out of 98) at 6 months and 56.12% (55 out of 98) at 15 months (Figure 3).

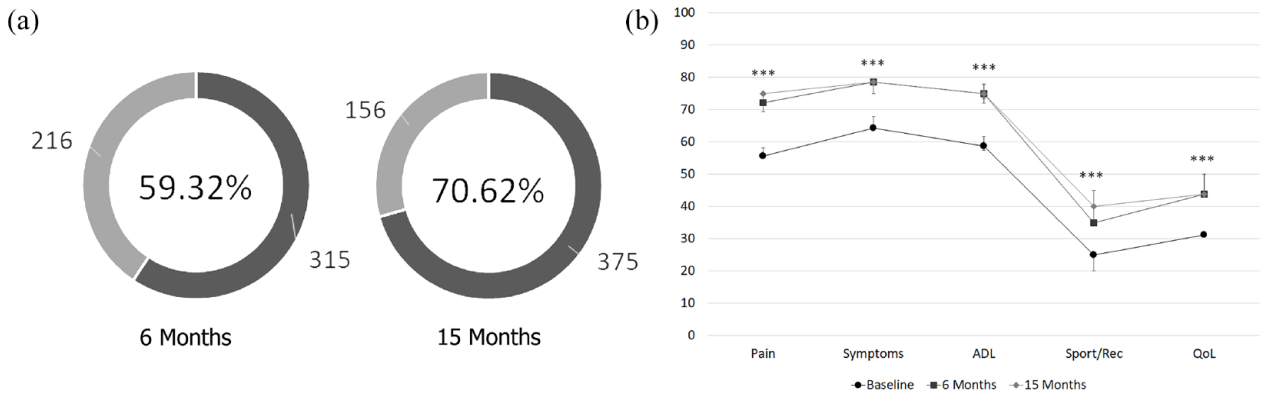

Figure 2. Overall effectiveness of platelet-rich plasma. Percentage of MCII patients at 6 and 15 months after treatment (a). KOOS scores before and after treatment (b).
ADL, activities of daily living; CI: confidence interval; KOOS, Knee injury and Osteoarthritis Outcome Score; MCII, Minimal Clinically Important Improvement; QOL, knee-related quality of life; Sport/Rec, function in sport and recreation.
Error bars: CI. *$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$.

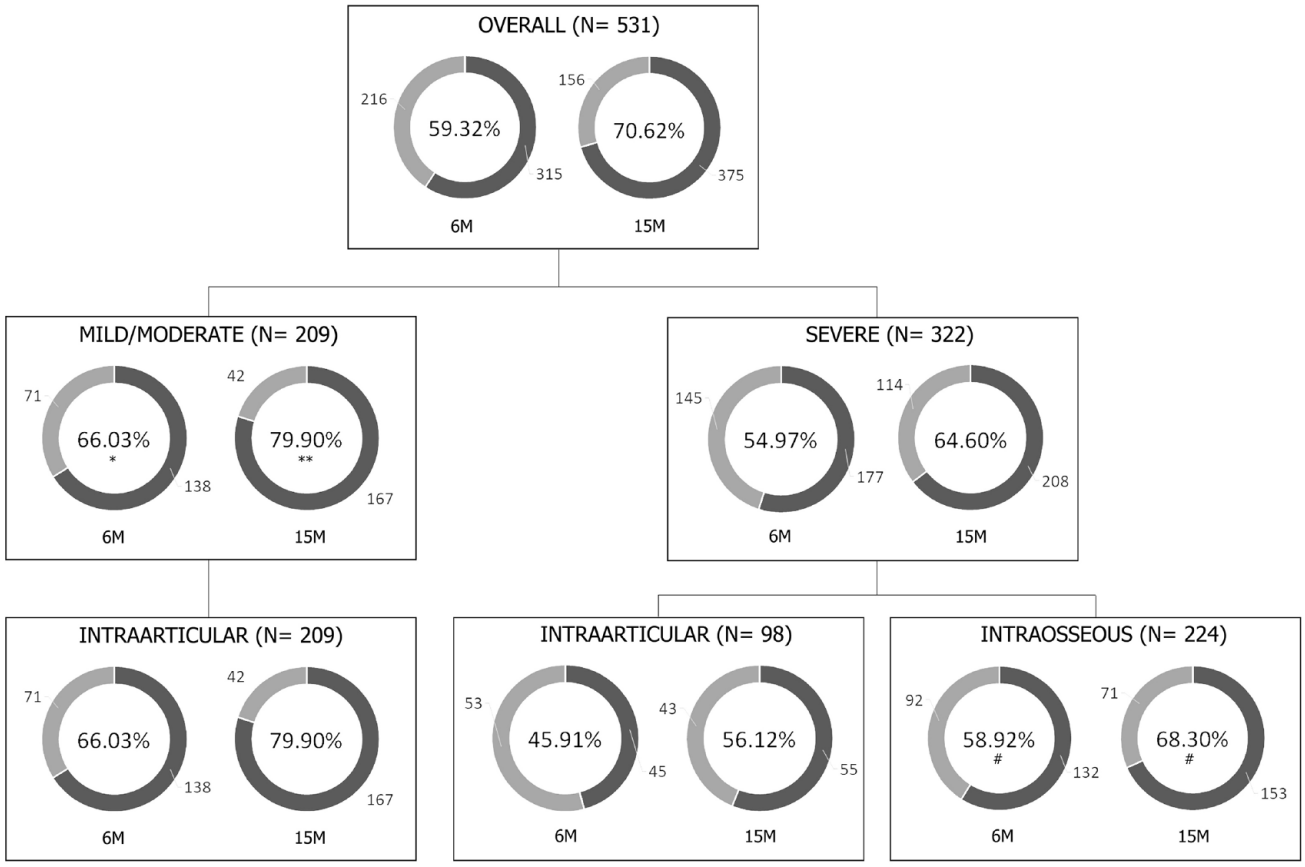

Figure 3. Percentage of patients with MCII according to severity and route of administration.
6M, follow-up at 6 months; 15M, follow-up at 15 months; MCII, Minimal Clinically Important Improvement.
*$p < 0.05$; **$p < 0.001$ with respect to severe cases; #$p < 0.05$ with respect to severe cases treated with intraarticular infiltrations.

The increase in KOOS scores was also significantly greater in mild/moderate cases than in severe cases (Figure 5(a) and (b)).

The effectiveness in treating severe pathologies was significantly improved when PRP was administered *via* intraosseous route. Of the 531 cases, 224

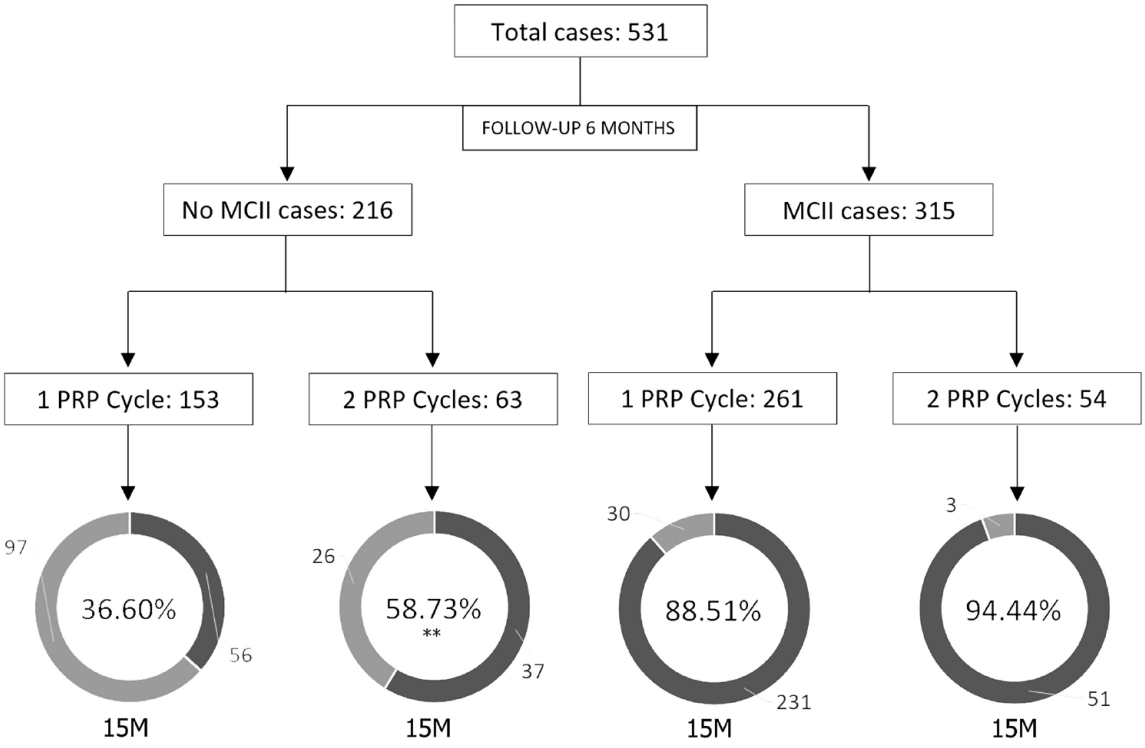

Figure 4. Percentage of patients with MCII according to number of cycles of PRP.
15M, follow-up at 15 months; MCII, Minimal Clinically Important Improvement; PRP, platelet-rich plasma.
*$p < 0.05$ with respect to the group receiving one PRP cycle.

received intraosseous treatment, all with severe pathology. When comparing the clinical outcome in severe pathology, the group receiving intraosseous PRP had an MCII rate of 58.92% at 6 months, 13.01 percentage points higher compared with patients receiving intraarticular treatment (CI: 1.19–24.39; $p = 0.0311$). The MCII rate at 15 months was 68.30%, 12.18 percentage points higher than the response to intraarticular PRP (CI: 0.82–23.59; $p = 0.0358$; Figure 3) (Supplementary Table S6). Increases in KOOS scores were also greater in cases treated with intraosseous PRP (Figure 5(c) and (d); Supplementary Table S7).

Bone marrow lesions

In 33 of the 531 cases, bone marrow lesions (BMLs) were detected by magnetic resonance imaging (MRI) and treated with intraosseous PRP. The average age of this group of patients was 49 ± 14.82 years with a BMI of 26.96 ± 4.25 and a female percentage of 42.42%.

The percentage of patients with MCII at 6 and 15 months post-treatment was 69.70% (23 out of 33) and 78.79% (26 out of 33), respectively. All KOOS scores improved significantly at both 6 and 15 months post-treatment ($p < 0.001$). During follow-up MRI studies, the decrease (41.94%) and removal (41.94%) of the BML image were observed (Figure 6).

Multivariate logistic regression

The multivariate logistic regression model indicated that medium/moderate severity ($p = 0.001$) and intraosseous application ($p = 0.024$) significantly favoured positive response to treatment at 6 months (Table 2). The 12-month model (Table 3) showed the strong influence of severity, with a better response in patients with mild/moderate pathologies ($p < 0.001$).

Discussion

The present study examines 531 cases of degenerative knee pathology treated with PRP and followed up for at least 1 year. The overall effectiveness of PRP was more than 70%, based on the percentage of patients with MCII. This response is influenced by patient, pathology, product and protocol (4P) factors. Thus, these 'four Ps' should

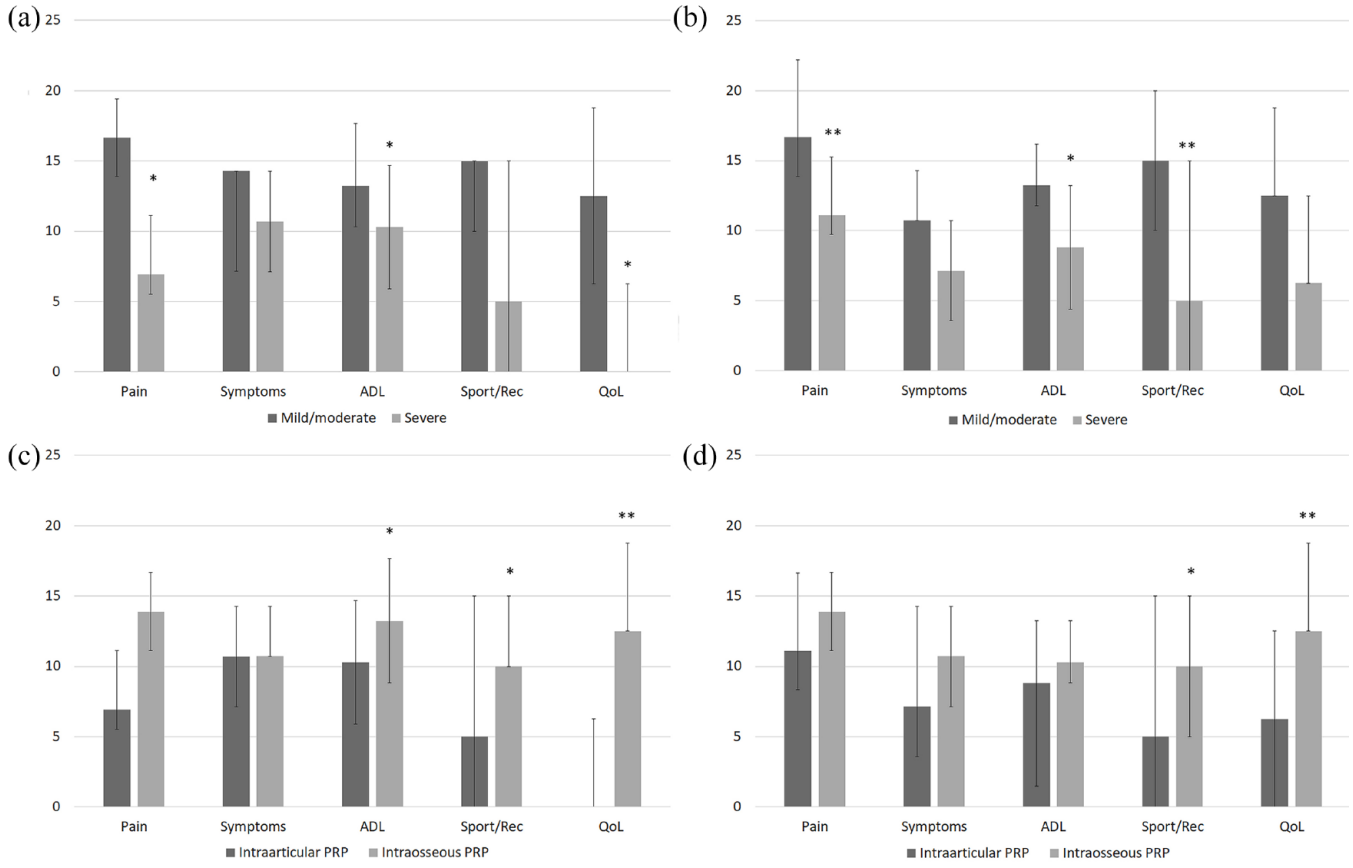

Figure 5. Differences in response according to severity and route of administration. Differences in the increase in KOOS scores according to severity after intraarticular PRP treatment at 6 (a) and 15 (b) months follow-up. Differences in the increase of KOOS scores according to the type of treatment in severe pathologies at 6 (c) and 15 (d) months follow-up.
ADL, activities of daily living; KOOS, Knee injury and Osteoarthritis Outcome Score; QOL, knee-related quality of life; Sport/Rec, function in sport and recreation.
Error bars: CI. *$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$.

be taken into consideration in order to achieve an optimal clinical outcome (Figure 7).

RWE studies are a valuable tool to analyse the effectiveness of treatment in a real scenario and the factors that may influence it. Although RCTs are essential to evidence-based medicine, they present several limitations that hinder this type of analysis. Concerning PRP, RCTs evaluate a limited number of subjects, and although they are subsequently examined in meta-analyses, the data obtained can be misleading due to the different PRP products and treatment protocols. In contrast, despite their inherent limitations, RWE studies reflect the response to treatment in the real world and allow us to reach a sufficient number of patients to analyse the different variables that could influence the response. The information obtained in both types of studies is useful in helping to find the best possible treatment.[9–11]

The present study is the prospective observational study to have analysed the largest number of patients to date. The results obtained align with the latest RCTs and meta-analyses published, indicating that PRP is an effective treatment for degenerative knee pathologies. Our work considers clinical outcome the results of the scores and their clinical significance according to the MCII, because a statistically significant difference in the scores does not mean a clinical one.[8,10–21] This is becoming increasingly important in the analysis[22] and allows a better interpretation.[23] It should be noted that the type of PRP applied to all the patients in the study was obtained using the same system and with the same cellular composition in accordance with the quality

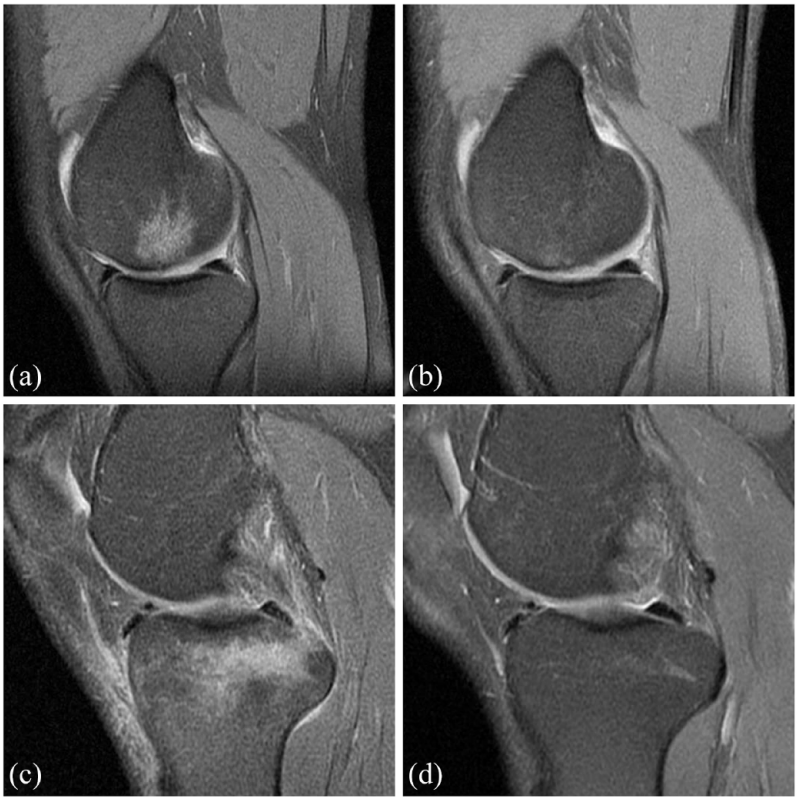

Figure 6. MRI images of BML. Before (a) and 15 months after (b) intraosseous PRP treatment of a BML in the medial femoral condyle. Before (c) and 15 months after (d) intraosseous PRP treatment of a BML in the tibial plateau.
BML, bone marrow lesion; MRI, magnetic resonance imaging.

control carried out, so it is a variable that did not interfere in the results analysed.

The only study with similar characteristics that can be compared with the present work was that carried out by Korpershoek *et al.*,[24] which analysed 158 cases treated with Autologous Conditioned Plasma (ACP). The authors obtained similar results to ours in terms of KOOS scores, with significant differences at 6 and 12 months from baseline. However, the MCII values are lower, which may be due to several factors such as patient characteristics. While the work of Korpershoek *et al.* focuses only on knee osteoarthritis, the present work encompasses all joint degeneration. We must underline the high efficacy (more than 90%) of the treatment in cases of chondromalacia patellae, which correspond to mild/moderate cases of patellofemoral pathology. Although the data obtained do not suggest the influence of location on the efficacy of the treatment, the typology of these patients,[25] with early degeneration, young age and low BMI, makes them highly suitable candidates for PRP treatment, as these are key factors in the response to treatment according to the data obtained. In the case of age, the enhanced response could be due to improved health and the molecular composition of the PRP.[26] Very few studies have evaluated the effect of PRP in chondromalacia patellae achieving good results both in imaging

Table 2. Multivariate regression analysis for response at 6 months.

Variable	*B*	*p* value	95% CI	OR
Age	−0.008	0.291	0.977–1.007	0.992
BMI	−0.017	0.408	0.943–1.024	0.983
Severity (mild–moderate/severe)	0.870	0.001*	1.397–4.076	2.387
Administration route (IA/IO)	−0.604	0.024*	0.324–0.923	0.546

B, coefficient; BMI, body mass index; CI, confidence interval; IA, intraarticular; IO, intraosseous; OR, odds ratio.
*$p < 0.05$.

Table 3. Multivariate regression analysis for response at 15 months.

Variable	*B*	*p* value	95% CI	OR
Age	−0.008	0.378	0.975–1.009	0.992
BMI	−0.039	0.086	0.921–1.005	0.962
Severity (mild–moderate/severe)	1.145	<0.001*	1.757–5.615	3.141
Administration route (IA/IO)	−0.473	0.088	0.362–1.073	0.623
PRP cycles	0.123	0.657	0.658–1.942	1.130

B, coefficient; BMI, body mass index; CI, confidence interval; IA, intraarticular; IO, intraosseous; OR, odds ratio; PRP, platelet-rich plasma.
*$p < 0.05$.

and clinical studies.[27–29] This treatment should be considered an option not only for the improvement of the patient but also to attempt to prevent more serious conditions such as patellofemoral osteoarthritis.

A second key factor is the type of product and the application protocol. Korpershoek *et al.* used ACP that is similar to that used in our study. This PRP does not present leukocytes and erythrocytes, which could make it the most suitable for this type of pathology.[30,31] However, the platelet concentration reached by Korpersoek *et al.* doubled ours and was applied in a volume of only 3–5 ml, compared with 8 ml in our protocol. It makes the number of platelets similar in each intraarticular infiltration (around 2.5×10^9) in a different volume. Furthermore, a recent RCT that failed to demonstrate the superiority of PRP *versus* placebo used a type of PRP with a large variability in concentration factor (1.6×–5×) and a volume of 5 ml.[32] Thus, not only the type of product but also the volume needs to be kept in mind. The intraarticular distribution of the PRP must be adequate and reach all the tissue, which is achieved with volumes of approximately 9 ml.[33] Guillibert *et al.*[34] observed that a high-volume (8 ml) administration of PRP achieved a clinical improvement of more than 80%, proposing this administration as a better alternative to repeated low-volume infiltration protocols. Furthermore, injecting smaller volumes would also lead to the delivery of less therapeutic content present in the plasma such as exosomes or other biomolecules.[35,36]

Regarding the treatment protocol, previous clinical studies suggest that repeated weekly PRP injections are more effective than a single dose.[37] In addition, kinetic studies showed a release of biomolecules from fibrin during 1 week.[38] However, the application of repeated PRP cycles over time is still little studied. According to the

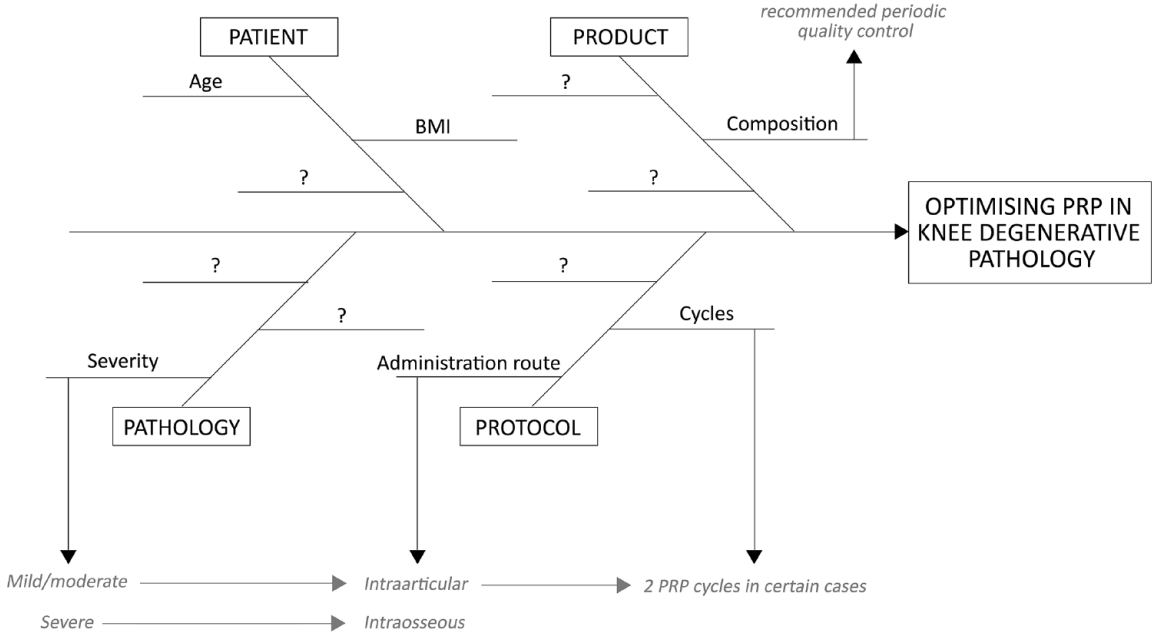

Figure 7. The 'four Ps' influencing the effectiveness of PRP. The clinical response to PRP treatment is influenced by many factors related to the patient, the pathology, the product and the protocol, many of which are still unknown. PRP, platelet-rich plasma.

present work, the effect of a second cycle after the first 6 months could be a useful recommendation in certain cases. In an RCT conducted by Vaquerizo *et al.*,[39] using the same PRP and the same protocol, the authors observed an improvement in symptoms and functionality in patients with two cycles, but not in pain, as in the present study. However, this occurred in cases that had not yet shown a positive clinical response at 6 months. In severe cases, it did not increase efficacy, being effective only in patients with mild/moderate pathology. Therefore, although the application of the second cycle of PRP would be advisable to enhance or accelerate the response in patients with mild/moderate pathology, severe pathologies present characteristics and a degree of complexity for which intraarticular application may be insufficient.[16] Patients with severe pathologies treated with intraosseous PRP showed a significant improvement compared with those who received only intraarticular PRP. In these cases, key tissues such as the subchondral bone are more greatly affected. The data obtained in the multivariate analysis confirmed the importance of the severity of the pathology, as well as the higher impact of the route of administration compared with the repetition of cycles. Direct application of PRP extends the range of action and acts on detrimental processes such as the growth of fibroneurovascular tissue, mesenchymal stem cell alterations or biomolecular imbalance.[40] Recent clinical studies suggest the effectiveness and safety of this technique and are consistent with the data obtained in this study, although further study of this route of administration is needed.[41] In fact, this administration could be used for other products such as cell concentrates, although in these cases numerous variables such as age, dosage, composition, protocol or adjuvant substances must be taken into consideration because, otherwise, optimal clinical results may not be achieved.[42] Intraosseous PRP in patients with BML was also shown to be highly effective in line with a recent study that showed a significant decrease in pain 1 year after treatment.[43] These subchondral bone lesions are associated with cartilage loss, and they can also be the origin of joint degeneration.

The effective results obtained in this work together with the limited adverse effects, characterized by episodes of pain in the infiltration area during the following hours, suggest that the reasonable application of PRP is a valid treatment in the management of these pathologies. Along with RCT and RWE studies, cost-effectiveness should also be taken into account for a full assessment of this treatment. Recent studies indicate that PRP could be cost-effective in the long term, although further research is needed.[44,45]

The limitations of this study are inherent to RWE studies, which lack the strengths of RTCs, namely, randomization, control and more specific follow-up times. The loss of patients during follow-up is considerable, hampering longer follow-ups which could provide important information as in previous studies,[46] and making it necessary for large-scale recruitment. Furthermore, despite a large number of patients, '*N*' was insufficient to draw solid conclusions for some subgroups. Finally, this type of study assesses clinical outcomes which may be due to an improvement in symptomatology rather than a modification of the disease. However, findings such as the disappearance of BML or reduction in joint effusion after treatment could suggest an effect on the origin of this pathology. Indeed, the presence of synovial fluid was reduced in more than 60% of patients after treatment, which could be a sign of a positive impact on the progression of the disease.[47] In this regard, a recent work conducted by Boffa *et al.*[48] reviewed *in vivo* studies demonstrating disease modification by PRP administration. Evaluation of these modifications in clinical research using imaging or surgical studies[46] would help to clarify the action of PRP and its mechanisms.

Conclusion

The application of PRP in degenerative knee pathologies is an effective treatment, but this effectiveness nonetheless depends on several variables. Far from considering PRP to be a magic bullet, the physician must consider certain variables related to the patient, the pathology, the product and the protocol to optimize this treatment. Complementing the information from RCTs with that obtained from RWE studies can be a valuable tool for advancing our understanding of PRP.

Ethics approval and consent to participate

Ethical approval for this study (Protocol No. EPA2015046) was obtained from the Ethics Committee of the Basque Country.

Consent for publication

Written consent was obtained.

Author contribution(s)

Mikel Sánchez: Conceptualization; Investigation; Methodology; Writing – review & editing.

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Acknowledgements

The authors wish to thank M.B. Sánchez, A. Iriondo, M. Montoya, M.J. Arnaiz and C. Pérez de Arrilucea for their involvement in the processing of the PRP samples.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data underlying this article are available in the article and in its online supplementary material.

Supplemental material

Supplemental material for this article is available online.

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