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Intraosseous infiltrations of Platelet-Rich Plasma for severe hip osteoarthritis: A pilot study

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ABSTRACT

Objective: Addressing the subchondral bone through intraosseous infiltrations of Platelet-Rich Plasma (PRP) may improve the effectiveness of this technique for severe hip osteoarthritis (HOA).
Methods: Forty patients with HOA degree 2 and 3 according to the Tönnis scale were recruited for this study. They were susceptible to a total hip arthroplasty, without response to previous treatment based on intraarticular infiltrations of PRP. Patients received a combination of intraosseous injections into the acetabulum and the femoral head, as well as intraarticular PRP infiltrations. The clinical outcome was evaluated at 2, 6 and 12 months using the Hip Osteoarthritis Outcome Score (HOOS) and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index.
Results: At 2, 6 and 12 months, patients had significant pain improvement according to HOOS pain, WOMAC pain, and VAS scores. After the treatment, the percentage of patients with minimal clinically important improvement was 40% (16 over 40 patients) at 2 months, 37.5% (15 over 40) at 6 months, and 40% (16 over 40) at 12 months. *Conclusion*: The combination of intra-articular and intra-osseous infiltrations of PRP showed a pain reduction and improvement in hip joint functionality up to 12 months in patients with severe HOA, with no severe adverse effects.

1. Introduction

Osteoarthritis (OA) is a degenerative musculoskeletal pathology which has become an issue of concern in worldwide health care due to its high prevalence. Approximately 40% of the population over 65 years old could develop osteoarthritic symptoms, and the hip is a commonly affected joint with a prevalence between 7% and 25% in white patients over 55 years of age.[1] The symptoms of hip osteoarthritis normally include pain and dysfunction, which reduce their quality of life. Moreover, the increase in life expectancy and obesity rates could raise the prevalence of this pathology. There is currently no effective treatment which stops the progression of OA, which leads to joint replacement and causes a risk for patients and a great cost for health systems.[2]

Current treatments such as physiotherapy, oral analgesics and anti-inflammatory drugs or intraarticular injections of hyaluronic acid and steroids only focus on relieving the symptoms of OA, but do not eradicate the cause of the disease. Although these methods are able to relieve symptoms, degeneration continues to progress and arthroplasty seems to be the only solution for patients. This alternative may cause complications and, due to its limited lifespan, new and more difficult surgical interventions need to be performed in the future. Thus, it is necessary to develop new treatments that slow down the progression of joint degeneration triggered by OA. In recent years, treatments based on regenerative medicine have emerged, such as Mesenchymal Stem Cells (MSC) and Platelet-Rich Plasma (PRP), in order to decrease OA evolution and to regenerate cartilage. Although these new techniques have not been able to completely fulfill the proposed goals, promising advances have been achieved in the last years.[3] Concerning PRP, it is an autologous therapy that consists in plasma with a high platelet concentration obtained from the patient's own blood. Thus, PRP is a source of active biomolecules and a transient autologous fibrin scaffold with a high versatility allowing its application to different pathologies.[4] In the case of OA, PRP contains several biomolecules and growth

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factors that act on the entire joint, modulating biological processes related to the development of OA.[5]

The translation of PRP to clinical application can generate controversial results since the success of this treatment is conditioned by several factors.[6] One of them is the administration route of PRP, which is usually applied intraarticularly in joints with OA. Intraarticular administration soaks the entire intraarticular space acting on the cartilage but it does not act on other key structures such as subchondral bone. Several studies reported a communication and synergy action between cartilage and subchondral bone, achieving an optimal function of the whole joint and homeostasis balance.[7] It is reasonable to consider the subchondral bone as a therapeutic target in the treatment of OA, and recent studies have demonstrated the efficacy and safety of conducting intraosseous PRP injections directly into the subchondral bone in patients with advanced knee OA.[8–10] However, this type of administration has not been studied in patients with HOA. In fact, although the results achieved so far are promising, clinical studies on PRP as a treatment for this condition are still few. Bearing this issue in mind, the aim of this work is to evaluate the efficacy and safety of the combination of intraarticular with intraosseous infiltrations in patients suffering from HOA with a high degree of severity.

2. Material and methods

2.1. Ethical approvals and informed consents

The present study was carried out in accordance with the international standard on clinical trials: Declaration of Helsinki in its latest revised version (XXXXX), and Good Clinical Practice Regulations (International Conference for Harmonization). Approval by the ethics committee of The Basque Country (protocol number: XXXXX) and written informed consent were obtained.

2.2. Patients

This prospective case series study included a total of 40 patients recruited from 2015 to 2016. Digitized radiographs of the affected hips were examined in order to determine the degree of OA according to the classification scheme developed by Tönnis. The recruited patients had OA degree 2 and 3 according to the Tönnis scale, and were susceptible to a total hip arthroplasty, as they had not responded to previous treatment based on infiltrations of intraarticular PRP. Pain at baseline was of at least mild intensity,>20/100 on a 100-mm visual analogue scale (VAS). Exclusion criteria were young patients aged <18 years, protrusioacetabuli, concentric femoral head migration, extensive surgery of the reference joint (i.e. osteotomies around the hip, open or arthroscopic osteochondroplasty for femoroacetabular impingement), excessive deformity (i.e. acetabular or femoral head dysplasia, collapse deformity and deformed femoral head sequelae of Perthes), concomitant rheumatic illness, poor general health that interfered with assessments, intraarticular (IA) injections of corticosteroids, hyaluronic acid or PRP and tidal lavage in the preceding 6 months. Symptomatic slow acting drugs were withdrawn before PRP treatment. Concurrent medications, such as paracetamol or NSAIDs, were permitted but discontinued 48 h before the follow-up and visual analogue scale (VAS), Hip disability and Osteoarthritis Outcome Score (HOOS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaires were collected. They received a combination of two intraosseous PRP infiltrations with the first intraarticular injection followed by two more IA injections in the following two weeks.

2.3. Platelet-Rich Plasma preparation

Eighty mL of venous blood was withdrawn into 9 mL tubes containing 3.8% (wt/V) sodium citrate and centrifuged at 580g for 8 min at room temperature (Biotechnology Institute BTI, Vitoria-Gasteiz, Spain). The 2 mL plasma fraction located just above the red fraction, but not including the buffy coat, was collected in a tube and carried to the injection room for use. This PRP contained a moderate concentration of platelets from 1.5- to 2.5-fold times the concentration of platelets compared with peripheral blood, depending on the platelet count and size as well as the hematocrit. No leukocytes are presented in this PRP preparation. In order to initiate the activation of platelet clotting, calcium chloride (10% wt/V) was added to the liquid PRP aliquots just before injection. According to PAW classification, it is P2-x-Bβ PRP.[11] All procedures were performed under sterile conditions.

2.4. Treatment

The first PRP administration included three different injections in different anatomical locations performed in the operating room. First, one PRP intraarticular injection was conducted, and afterward two PRP intraosseous injections were performed according to the technique described by Fiz et al.[12] Briefly, under anesthesiologist surveillance, sedation of the patient was induced. An intraarticular injection guided by ultrasound was conducted using an 18-gauge needle oriented in the same direction as the anterolateral-distal arthroscopic portal. With a 30° of joint flexion to facilitate the infusion of the PRP infiltration, 8 mL of PRP was injected into the joint space.

Next, with the guidance of a fluoroscope, an anterior-posterior view of the hip joint was reached in order to perform the first intraosseous infiltration into acetabulum. The trocar was placed in the cranial-caudal direction, parallel to the horizontal plane and at an inclination of 20°. Once the trocar was introduced into the lateral acetabular wall and situated 1 cm from the articular line, five mL of PRP was injected. Finally, the second intraosseous injection was performed into the femoral head whose point of entry was situated 1 cm lateral to the sartorial muscle. The femoral head was approached at the union of the femoral neck and head, with the trocar orientated in the anterolateral-distal direction. The trocar was introduced 1 cm from the joint line, and 5 mL of PRP was injected. Intraosseous infiltration did not focus on specific lesions but was performed at the same point in all interventions, since PRP allocates all over the subchondral area regardless of tissue lesions (Fig. 1).[7] Once the procedure is complete, sterile drapes are removed, the skin is cleaned and wound dressings are applied at the infiltration points. Ice is then applied to the site. During the first few hours after treatment, assisted walking with crutches and a minimal initial load was recommended due to the intervention itself. Next days, the patient can bear weight and take analgesics (acetaminophen) as required for pain, with limited physical activity. Two more intraarticular PRP infiltrations were performed 14 and 21 days after the first treatment. Forty-eight hours after each intra-articular injection the patient can resume a daily routine with normal physical activity.

2.5. Outcome evaluation

Patients filled out questionnaires at baseline, 6 months and 12 months after the third intraarticular injection, and were evaluated by a different physician than the one who applied the treatment.

The primary efficacy criterion was a change from baseline in joint pain, measured using the HOOS pain subscale. Secondary efficacy variables included changes in VAS, HOOS subscales for

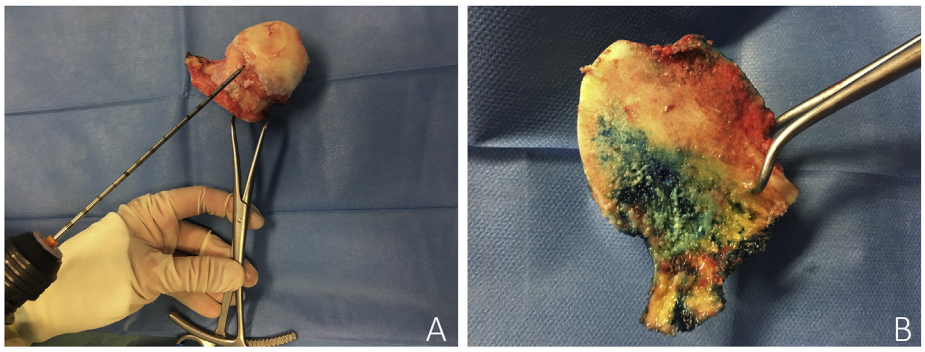

Fig. 1. Distribution of PRP after intraosseous injection. When PRP is administered intraosseously at the injection site such as the femoral head (A), the PRP diffuses and spreads throughout the tissue (B). In this case the PRP was stained with methylene blue.

symptoms, ADL, function in sport and recreation (Sport/Rec), knee related quality of life (QOL), as well as the WOMAC subscales for pain, stiffness and physical function. In the case of patients who failed to improve and underwent other treatments before 12 months, their basal values were included to obtain the score at this time-point. To evaluate the safety of the treatment, all complications and adverse events were assessed and reported during patient visits.

2.6. Statistical analysis

Power analysis was conducted to estimate the sample size needed to achieve 90% power at a 5% level of significance for the primary outcome measures. An assumed effect size of 10 points (minimal clinically important improvement, MCII)[13] with a standard deviation (SD) of 15 points was used. This analysis suggested a minimum of 34 patients, expecting a dropout rate of 0.3. Demographic and medical variables (gender, age, BMI and OA grade) were determined by the mean, standard deviation, range and percent. Comparisons were performed by Student's t-test for paired-samples parametric data and Wilcoxon signed-rank test for paired-samples non-parametric data. The distribution of the samples was assessed by Saphiro-Wilk test. Data were considered statistically significant when $p < 0.05$. Statistical analysis was performed with SPSS 17.0 (SPSS, Chicago, IL).

3. Results

Table 1 displays demographic data. Thirty of the forty patients included in the study were men (75%) and ten were women (25%), with a mean age of 45.63 ± 13.08 years (range: 21–70 years) and a mean BMI of 25.30 ± 3.08 (19,35–30,05). Eighteen patients were diagnosed with Tönnis II and 22 with Tönnis III, without positive response to previous treatments. No significant differences were found between the basal scores of patients with Tönnis 2 and Tönnis 3 ($p > 0.05$).

Table 1
Demographic characteristics.

N	40
Age, years	
Mean	45.6 ± 13.1
Range	21–70
Sex, *n* (%)	
Male	30 (75.0)
Female	10 (25.0)
BMI (kg/m^2)	
Mean	25.3 ± 3.0
Range	19.4–30.5
Tönnis grade n (%)	
II	18 (45.0)
III	22 (55.0)

3.1. Short-term clinical outcome

At two and six months after treatment, patients had significant pain improvement according to HOOS pain ($p < 0.05$) WOMAC pain ($p < 0.05$) and VAS ($p < 0.05$) scores. Moreover, this improvement was also obtained in the other variables related to symptoms and function assessed by the HOOS and WOMAC scales, except from WOMAC stiffness score (Table 2).

Regarding the percentage of patients with MCII according to the HOOS pain subscale, the treatment led to pain reduction of at least 10 points in 40% of patients (16 over 40) at two months, and 37,5% (15 over 40) at six months.

When comparing the scores between the Tönnis 2 and Tönnis 3 patients, no significant differences were found in the results ($p > 0.05$).

3.2. Long-term clinical outcome

Eight patients withdrew from the follow-up before the 12 months, 6 of which did not respond well to the treatment and underwent a total hip arthroplasty (15% of the 40 patients who were treated). Five of these 6 people who had to undergo surgery were diagnosed with Tönnis 3 OA. The 2 remaining patients, who were not monitored at 12 months, were unreachable.

The results related to pain displayed a significant improvement at 12 months according to the HOOS ($p < 0.05$), WOMAC ($p < 0.05$) and VAS ($p < 0.05$) scales. Patients also improved significantly in the variables related to symptomatology and function according to the HOOS and WOMAC scales (Table 2). In this case, there were no differences between the two severity degrees of HOA. The percentage of patients who showed a pain reduction of at least 10 points (MCII) from baseline to 12 months of follow-up was 40% (16 over 40 patients). When the clinical outcomes are compared between follow-ups, there is an improvement over time as the pain decreases significantly at 12 months with respect to 6 months according to the HOOS ($p < 0.05$) and WOMAC ($p < 0.05$) scales (Fig. 2).

3.3. Safety data

Patients who underwent intraosseous infiltrations did not refer side effects and complications during the procedure. After the infiltration, most of the patients reported mild pain of short

Table 2
Evolution of patients at time-points.

	Baseline	Two months		Six months		Twelve months	
	Score	Score	*p*	Score	*p*	Score	*p*
HOOS Pain	57.0 ± 16.3	63.9 ± 14.7	*0.002**	63.7 ± 17.5	*0.006**	67.7 ± 17.2	*<0.001**
HOOS Symptoms	58.1 ± 17.1	63.6 ± 15.8	*0.012**	64.3 ± 16.5	*0.009**	66.5 ± 16.9	*<0.001**
HOOS ADL	60.1 ± 18.4	68.4 ± 18.4	*0.002**	69.1 ± 19.6	*0.003**	70.7 ± 19.4	*<0.001**
HOOS Sport/Rec	39.4 ± 22.4	48.9 ± 22.7	*0.015**	48.6 ± 27.9	*0.046**	55.6 ± 24.8	*<0.001**
HOOS QOL	36.1 ± 20.6	40.9 ± 17.9	*0.92*	40.2 ± 20.1	*0.186*	42.7 ± 22.2	*0.054*
WOMAC Pain	64.4 ± 16.4	71.8 ± 16.7	*0.003**	69.6 ± 17.0	*0.033**	73.5 ± 17.2	*0.001**
WOMAC Stiffness	56.6 ± 21.6	62.2 ± 15.6	*0.057*	62.5 ± 17.9	*0.068*	65.6 ± 19.8	*0.003**
WOMAC Function	59.5 ± 18.9	68.4 ± 18.4	*0.001**	69.1 ± 19.6	*0.003**	70.5 ± 19.2	*<0.001**
VAS	4.5 ± 1.4	4.0 ± 1.4	*0.012**	3.6 ± 1.8	*0.002**	3.4 ± 1.7	*<0.001**

HOOS: Hip injury and Osteoarthritis Outcome Score; ADL: Function in daily living; Sport/Rec: Function in sport and recreation; QOL: knee related Quality of life. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; VAS: visual analogue scale.
*p < 0.05 respect to basal level.

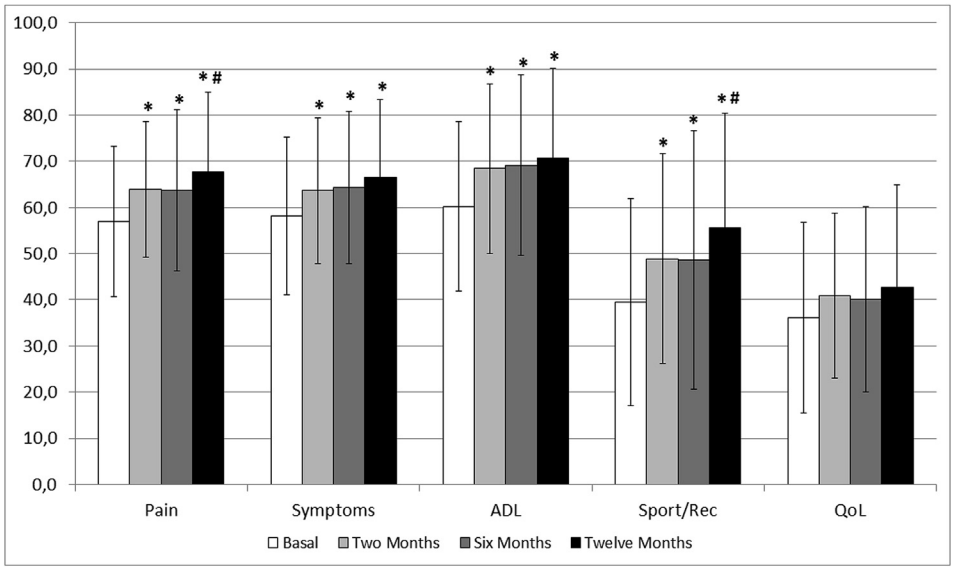

Fig. 2. HOOS scores at baseline, two months, six months and twelve months after treatment. HOOS: Hip Osteoarthritis Outcome Score; ADL: Function in daily living; Sport/Rec: Function in sport and recreation; QOL: Quality of life. *p < 0.05 respect to basal level.#p < 0.05 respect to six months level.

duration (24–48 h) and sensation of heaviness with no other adverse effects.

4. Discussion

The purpose of this work was to evaluate the efficacy and safety of the combined administration of intraosseous and intraarticular injections of PRP in patients with very advanced HOA for the first time. This technique is intended to include subchondral bone as a therapeutic target when treating this condition. The most important results of the study were an improvement in function and symptoms, especially in the scores related to pain, at 2 and 6 months after treatment. This improvement was maintained one year after receiving the treatment, and, what is more, the pain improvement increased compared to that observed after 6 months.

There are several works in the literature that evaluate the therapeutic action of PRP on HOA. The findings in those studies support the improvement in patients treated with IA infiltrations of PRP, especially in the early stages, because the treatment relieves inflammation and pain.[1,2,14–17].The trend in the results was similar, i.e. they lost effectiveness in the long-term and with patients with advanced osteoarthritis. These studies have slight variations in their methodological procedures to obtain PRP and consequently, PRP products with different compositions and characteristics. In this work the PRP used is type P2-x-Bβ PRP according to the PAW classification, with a platelet concentration approximately double the concentration in blood, and without the presence of leukocytes.[11] Although the effectiveness of different types of PRP in musculoskeletal pathologies is currently one of the most studied and controversial issues, the choice of the most optimal PRP for the treatment of joint pathologies is being elucidated.[18] According to recent studies, a platelet concentration below 5 fold blood platelet concentration and without leukocytes could be some of the ideal characteristics for its application in joint degeneration. An excessive number of platelets could inhibit the effect on tissue repair of PRP[19] as well as the presence of leukocytes has shown activation of pro-inflammatory pathways.[20] Apart from variables in the composition of the PRP, the application method must be also considered. In the present work, the PRP was applied on three separated occasions according to the recent studies that supported the several repeated administration of PRP. These studies focused on analyzing the differences between a single infiltration or several repeated infiltrations every one or two weeks, achieving better clinical response in patients who received repeated infiltrations.[21–23]

Different PRP mechanisms might explain the improvement of the symptomatology. Biomolecules within PRP such as HGF or platelet microparticles participate in the anti-inflammatory action

related to the inhibition of the intracellular NFκB pathway,[20] which is involved in cellular pro-inflammatory processes, and increasing the presence of M2 macrophages phenotype, leading to reparatory functions instead of the inflammatory response.[24] PRP also targets the endogenous cannabinoid systems acting as ligands for cannabinoid receptors 1 (CB1) and 2 (CB2) because of endogenous cannabinoids within PRP.[25] Nevertheless, the effectiveness seems to diminish over time and it is limited by the OA degree of patients, with those with the most severe conditions showing the worst response. The addition of intraosseous injections of PRP in order to reach the subchondral bone could help to overcome this drawback, and this approach has been applied in other pathologies such as avascular necrosis of the hip.[26] The results in the present work showed an improvement in symptoms at least up to 12 months, especially in the pain suffered by patients. In addition, all recruited patients presented HOA in its most advanced stage and had not responded to other conservative treatment treatments such as intraarticular infiltrations of PRP and total hip arthroplasty was the most likely indication.

The addition of PRP intraosseous infiltrations to conventional intraarticular administration lies in the importance of the subchondral bone for the development of osteoarthritis. Several studies have reported on the existence of communication between this tissue and cartilage by means of vessels and molecular channels, which is increased in patients with OA due to structural changes typical of this pathology such microcracks and fissures in the osteochondral junction.[27] The synergy of all the joint tissues allows the maintenance of homeostasis in the hip. An imbalance in any of these structures creates a vicious circle that leads to the degeneration of the joint involving different biological processes. MSC present in the subchondral bone are one of the essential elements in the maintenance of this tissue as well as cartilage. Campbell et al. observed an increase in the number of subchondral bone MSC that had an abnormal function and gene expression in patients with advanced OA, suggesting that the subchondral bone is a key therapeutic target.[28] In addition, overexpression of certain molecules in subchondral bone such as TGF-β1 also negatively influences the behavior of MSC. Zhen et al.[29] inhibited the activity of TGF-β1 on nestin positive-MSCs present at subchondral bone, which led to aberrant bone formation. As a result they reduced the degeneration present in the cartilage caused by OA. Thus, the biological action of PRP could modulate these cells when it is injected directly into the subchondral bone through intraosseous infiltration. In a study performed in patients with knee OA, a decreasing in the number of MSCs in the synovial fluid was observed after intraosseous infiltration of PRP, suggesting its possible modulating action. On the contrary, this decrease did not occur when it was administered only into the intraarticular space.[30]

Combining intraarticular injections of PRP with intraosseous administration makes the range of PRP reach more tissues and joint structures involved in the development of OA. Although biological treatments have not yet proven to stop and completely reverse this pathology, both alleviating the symptoms and slowing down the progress of degeneration means a promising opportunity that other conservative treatments do not offer. Thus, patients could benefit from a better quality of life for longer, achieving a delay in the joint replacement.[31]

It has to be considered that no other conservative treatment was indicated for these patients due to the severity of the OA. Indeed, these patients had not had any positive response to previous treatments. In addition, essays such as magnetic resonance images or histology were not carried out, which could explain the improvement in symptoms mechanistically or may suggest a structure-modifying disease intervention with this technique. Despite these limitations, the present pilot study evaluates the effect of treatment under the conditions of the routine clinical practice reflecting real patient population with severe HOA, avoiding the clinical restrictions of a randomized controlled trial.

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Declaration of competing interest

The authors declare no conflict of interest.

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