Technical Note

Intraosseous Infiltration of Platelet-Rich Plasma for Severe Hip Osteoarthritis

Nicolás Fiz, M.D., Juan Carlos Pérez, M.D., Jorge Guadilla, M.D., Ane Garate, Ph.D., Pello Sánchez, M.Sc., Sabino Padilla, M.D., Ph.D., Diego Delgado, Ph.D., and Mikel Sánchez, M.D.

Abstract: This work describes a technique of platelet-rich plasma (PRP) infiltration for the treatment of severe hip osteoarthritis (OA). Although the results achieved with intra-articular infiltrations of PRP are promising, they may be insufficient in the long-term for severe hip OA. The technique consists of a combined intra-articular and intraosseous infiltration of PRP to reach all joint tissues, especially the subchondral bone, and hence facilitate a greater distribution of PRP. Diagnosis is based on clinical and radiographic findings, and patients with grade III OA according to the Tönnis scale, as well as patients who have not responded to conventional treatment, are considered candidates for this technique. After an ultrasound-guided intra-articular PRP infiltration is performed, 2 intraosseous infiltrations are conducted with a fluoroscope; the first injection is applied into the acetabulum and the second into the femoral head. However, this technique presents more difficulty than the conventional administration, so it is necessary to consider several aspects described in this work.

After osteoarthritis (OA) of the knee, the hip ranks as the second most affected joint, with a high prevalence in patients older than 50 years. Although OA is not a life-threatening condition, the severity of this disease lies in the continuous pain and functional impairment that patients undergo, undermining their quality of life. Formerly, the basic theory to understand and deal with this disease was cartilage loss. Including oral drug treatment and intra-articular injections of hyaluronic acid and steroids, the conservative treatments used to date have merely relieved the symptoms but do not stop or slow the natural course of the disease. As a result, total hip replacement is often the only solution for patients with hip OA.[1,2]

In an attempt to improve present-day treatments, techniques based on regenerative medicine have been introduced using intra-articular infiltrations of platelet-rich plasma (PRP).[3-5] This biological therapy uses the patient's own blood to obtain a product in which platelets are found at higher concentrations than in blood and mainly convey fibrin and growth factors as effectors. PRP-based therapies have broken into the clinical practice of many medical specialties, especially the field of orthopaedics and sports medicine; proof of this are the increasing studies for pathologies such as OA, tendinopathy, or ligamentous injuries.[6] In the case of PRP use in OA, growth factors have inductive and protective effects on chondrocyte and anti-inflammatory action, restoring joint homeostasis.[7] Although the results achieved thus far are promising and many patients will undoubtedly benefit from these cutting-edge interventions, treatments are still focused on cartilage as the main therapeutic target and they may be insufficient in the long-term for severe hip OA.

Currently, cartilage loss is not considered the key pathologic process that triggers OA. Rather, the initiating factor seems to be the result of a malfunction present in the whole joint, including all tissues crucial for maintaining articular homeostasis. Subchondral bone is identified as the starting place for pathologic changes, and cartilage is the victim of this process. Lesions in this tissue lead inevitably to the onset of OA if they are not properly treated.[7] By means of the technique described

From the Arthroscopic Surgery Unit (N.F., J.C.P., J.G., M.S.) and Advanced Biological Therapy Unit (A.G., P.S., D.D., M.S.), Hospital Vithas San Jose; and Biotechnology Institute (S.P.), Vitoria-Gasteiz, Spain.

The authors report the following potential conflict of interest or source of funding: S.P. receives support from Biotechnology Institute (BTI).

Received October 9, 2016; accepted February 15, 2017.

Address correspondence to Diego Delgado, Ph.D., Advanced Biological Therapy Unit, Hospital Vithas San Jose, Vitoria-Gasteiz, C/Beato Tomás de Zumárraga 10, 01008 Vitoria-Gasteiz, Spain. E-mail: diego.delgado@ucatrauma.com

2212-6287/16970/$36.00

http://dx.doi.org/10.1016/j.eats.2017.02.014

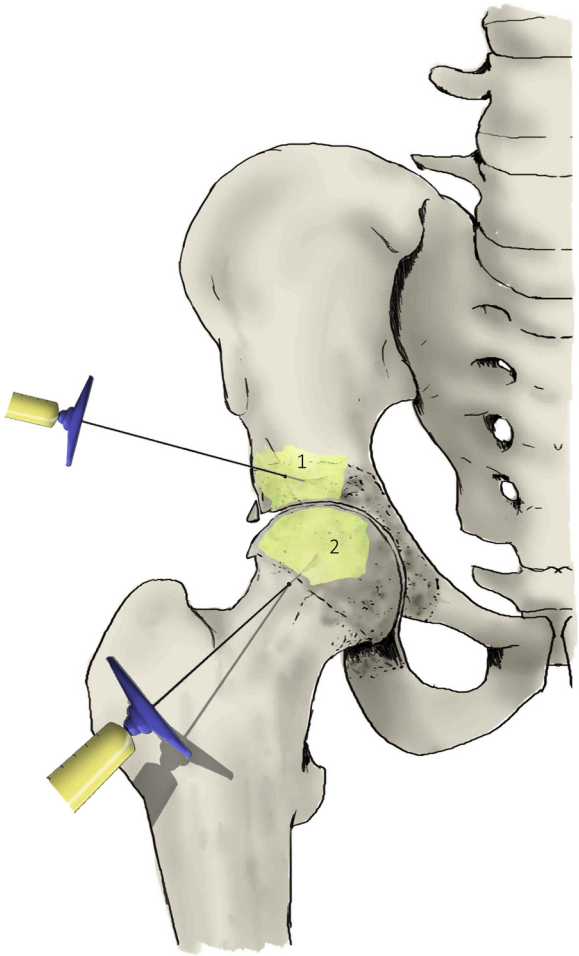

Fig 1. In a right hip (anterior view) with severe osteoarthritis, intraosseous platelet-rich plasma infiltration is performed into the acetabulum (1) and femoral head (2). Before these intraosseous injections are performed, a conventional hip intra-articular infiltration of platelet-rich plasma is conducted.

in this work (Video 1), we propose delivering PRP by combining intraosseous infiltrations (Fig 1) with intra-articular injections to reach the highest percentage of hip tissue, namely cartilage, synovial membrane, and subchondral bone, and thus enhance the therapeutic reach of PRP, extending its effect.

Surgical Technique

Diagnosis

Diagnosis of OA is based on clinical and radiographic findings. The radiographs used are the weight-bearing anteroposterior (AP) view of the pelvis (Fig 2A) and the axial view of Lowenstein (Fig 2B). Patients with grade III OA based on the Tönnis scale are considered candidates for this technique (Fig 2C).

PRP Preparation

Before sedation is induced, about 80 mL of venous blood is extracted from the patient to prepare the PRP according to PRGF-Endoret technology (Biotechnology Institute [BTI], Vitoria-Gasteiz, Spain). In brief, blood is centrifuged at 580 *g* for 8 minutes at room temperature. The 2-mL plasma fraction located just above the sedimented red blood cells, but not including the buffy coat, is collected in a tube and carried to the injection room for use. To initiate the activation of platelet clotting, calcium chloride (10% wt/vol) is added to the liquid PRP aliquots just before injection. All procedures are performed under sterile conditions.[8]

Patient Preparation

Sedation (Table 1) is performed by infusing a single dose of normal saline solution, as well as a single dose of midazolam (0.03-0.05 mg/kg) and fentanyl (3.2 mg/kg), in the peripheral vein; a single or repeated dose of propofol is also administered (1-2 mg/kg), depending on the duration of the infiltration. The degree of sedation is −4 or −5 on the Richmond Sedation Scale. The patient is positioned supine on the operating room table. Position references are drawn on the skin of the patient, namely, the anterior superior iliac spine and the greater trochanter. The joint line itself is also drawn by use of radiographic assistance with a fluoroscope on an AP view. Once the position is mapped, the infiltration area is prepared with a povidone-iodine solution, covering a region 10 cm proximal and 10 cm distal to the infiltration zone. Sterile drapes defining the treatment zone are put in place.

Intra-articular Infiltration

Infiltration is guided by ultrasound (Table 1). When the head of the femur has been located, the ultrasound probe is directed toward the median of the femoral neck (Fig 3A). To perform the intra-articular infiltration of PRP, an 18-gauge needle is used, oriented in the same direction as the anterolateral-distal arthroscopic portal. The needle is directed toward the transition zone between the head and the neck of the femur to avoid causing a lesion in the acetabular labrum (Fig 3B). Once the needle has been inserted into the joint space, 8 mL of PRP is injected. It is recommended to perform the infiltration in 30° of joint flexion, which will open the anterior capsule of the hip joint, thereby facilitating the infusion of the PRP infiltration.

Intraosseous Acetabular Infiltration

The intraosseous infiltration is performed with the guidance of a fluoroscope (Table 1), which provides the AP view of the hip joint. An 11-gauge bone biopsy trocar is introduced 3 cm proximal to the joint line previously drawn and in line with the anterolateral arthroscopic portal. The trocar is placed in the cranial-caudal direction, at an inclination of 20° and parallel to the horizontal plane, and is pushed until the lateral acetabular wall is reached (Fig 3C). The acetabular bone

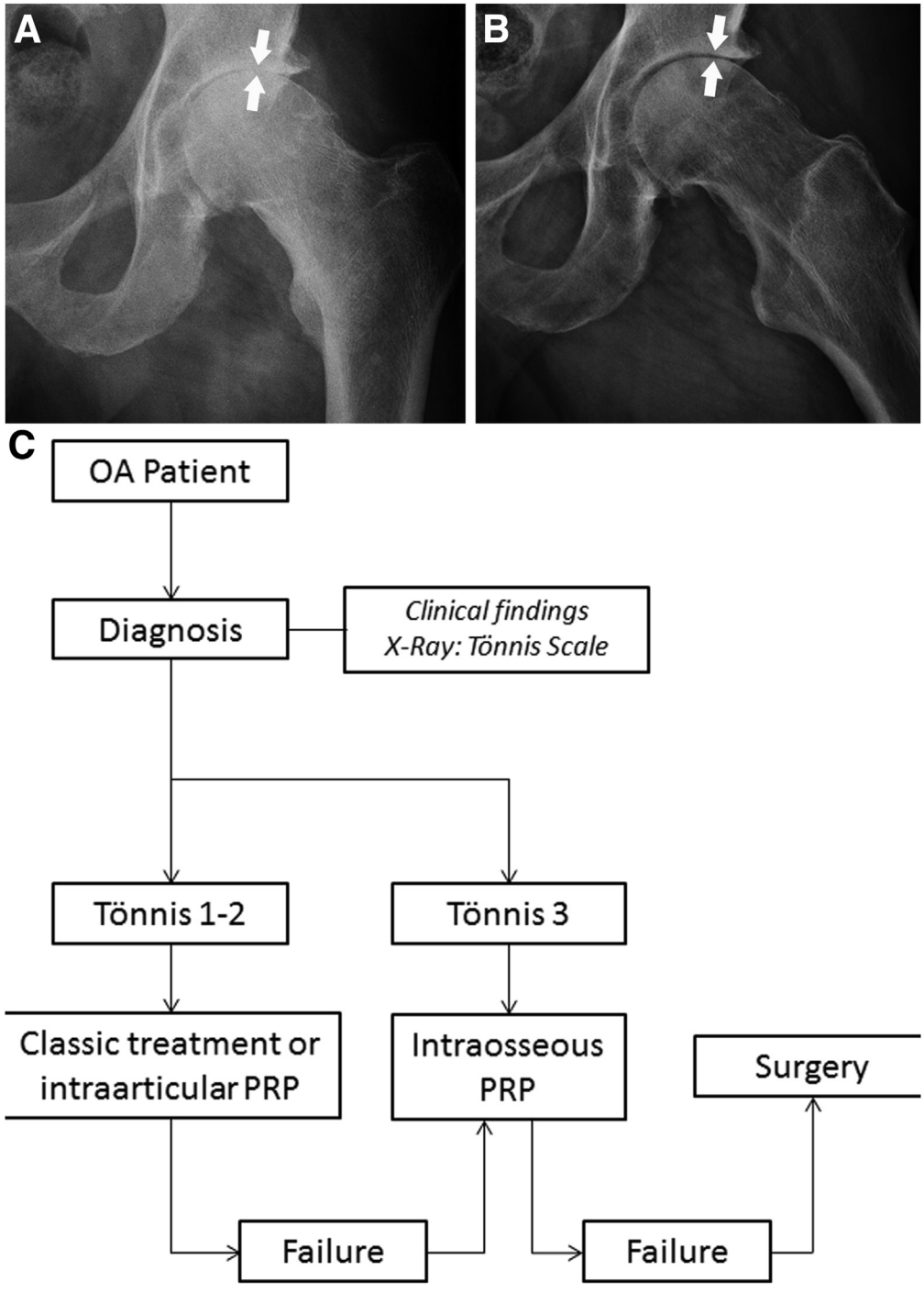

Fig 2. Patients are diagnosed with osteoarthritis (OA) by a physical examination and imaging techniques using weight-bearing anteroposterior (A) and axial (B) radiographs, on which joint space narrowing can be observed (arrows), as well as the Tönnis scale. (C) Depending on the OA grade, different treatments can be applied. If the patient presents with Tönnis grade I or II, we propose a classic treatment or intra-articular infiltrations of platelet-rich plasma (PRP). If conventional treatment fails in grade III patients, we apply intraosseous infiltration and 2 more intra-articular infiltrations in the following weeks. If the treatment fails or the patient presents with grade IV, he or she undergoes a surgical intervention.

on this side is hard and resistant, so infiltration can be difficult; the inclination used for this infiltration helps us to penetrate into the bone. It also allows us to control the placement of the trocar close to the subchondral bone. With the help of a hammer, the trocar is introduced into the acetabulum, until it is situated 1 cm from the articular line (Fig 3D). Five milliliters of PRP is then introduced intraosseously.

Intraosseous Femoral Infiltration

Following the direction of the anterior arthroscopic portal, the 11-gauge trocar is introduced into the head of the femur. The point of entry on the skin is situated 1 cm lateral to the sartorial muscle to avoid lesions of the femoral cutaneous nerve during the infiltration (Fig 3E). The trocar placement is oriented in the same direction as the anterolateral-distal arthroscopic portal. The entry

Table 1. Pearls and Pitfalls

Intra-articular infiltration is performed at the base of the femoral neck and must be guided by ultrasound.
The use of a fluoroscope is recommended to perform intraosseous infiltrations.
The patient is under sedation during the process.
In case of an infection due to intraosseous infiltration, its treatment will be more complicated to resolve.

point on the femoral head is at the union of the femoral neck and head to prevent damage to the articular cartilage. With the assistance of the hammer, the trocar is introduced 1 cm from the joint line (Fig 3F). Five milliliters of PRP is then introduced intraosseously.

Finally, after completion of the infiltrations and removal of the sterile drapes, the skin is cleaned with an alcohol solution, and wound dressings are applied at the infiltration points. Ice is then applied to the site. In the days after surgery, the patient can bear weight and take analgesics (acetaminophen) as required for pain. Two more intra-articular PRP infiltrations of 8 mL each are performed 7 and 14 days after the first treatment, by use of the described technique.[4]

Discussion

OA is a prevalent and disabling disease, and the hip is one of the joints most affected by this pathology. Current treatments only relieve symptoms and do not stop the course of the disease, and this often forces the patient to undergo a total hip replacement.

Treatments that stop or slow OA are necessary to prevent or delay surgery, improve the quality of life, and avoid the economic costs of this condition.[1,2] The results obtained with intra-articular injections of PRP to treat hip OA confirm this technique as a promising therapeutic alternative,[3-5] but they only reach the hip intra-articular space and they may not be effective in severe or advanced OA. This double administration of PRP combines intra-articular infiltrations with intraosseous injections aimed at the subchondral bone of the anterior superior iliac spine and greater trochanter. In this way, PRP reaches the most tissues involved in this pathology and it may achieve a better response in severe hip OA.

Conducting intraosseous PRP infiltrations has the challenge of taking more time and involving recently described techniques compared with conventional intra-articular infiltrations. It involves sedation and local anesthesia because the subchondral bone injection generates a pressure increment inside the bone, which could cause pain 48 hours after treatment.

The use of fluoroscopic control is also recommended for a proper administration. Thus it is necessary to train the medical team and spend more time on this type of intervention, making it more expensive than conventional infiltrations into the hip.

However, the benefits of combining intra-articular and intraosseous infiltrations of PRP far exceed the

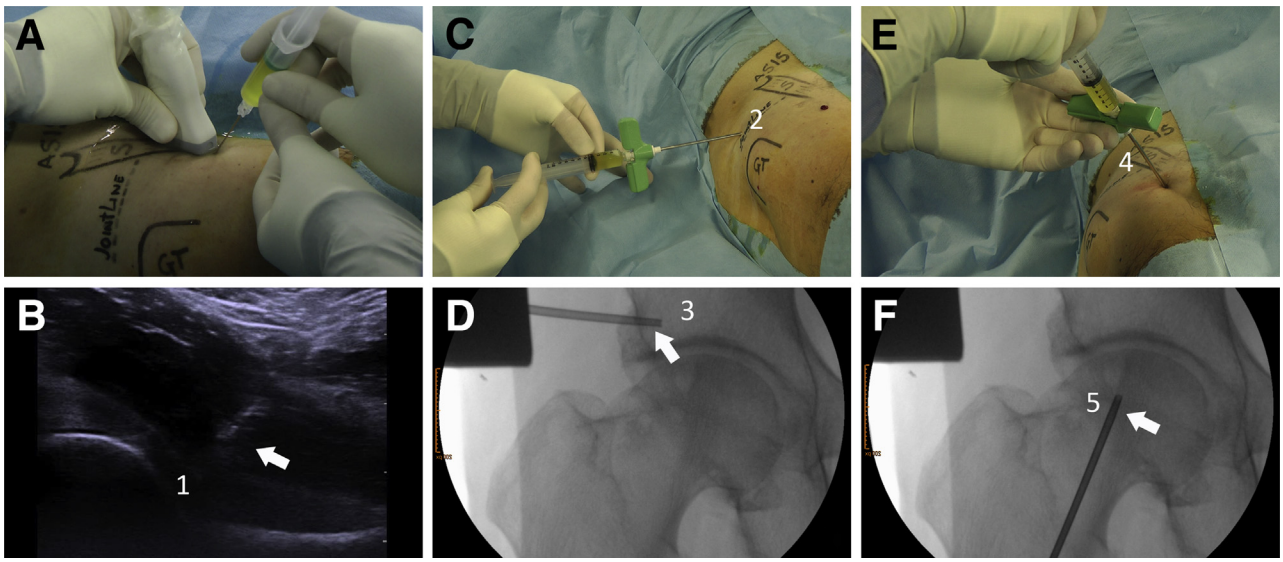

Fig 3. (A) After the patient is positioned supine on the operating room table, ultrasound-guided intra-articular infiltration is performed into the joint and an ultrasound probe is directed toward the median of the femoral neck. (B) An 18-gauge needle (arrow) is directed toward the transition zone between the head and the neck of the femur (1). (C, D) Intraosseous acetabular infiltration is conducted in the cranial-caudal direction (2), with the trocar (arrow) placed at an inclination of 20° and parallel to the horizontal plane. It is introduced into the acetabulum, until it is situated 1 cm from the articular line (3). (E, F) Concerning intraosseous femoral infiltration, the trocar (arrow) placement is oriented in the same direction as the anterolateral-distal arthroscopic portal. It is applied 1 cm lateral to the sartorial muscle (4) and introduced 1 cm from the joint line at the union of the femoral neck and head (5).

Table 2. Advantages and Disadvantages

The range of action of PRP is extended.
The technique allows direct action over subchondral bone.
The technique modulates the mesenchymal stem cells of subchondral bone.
The technique is applicable to pathologies in which subchondral bone is involved.
Difficulty, time, and costs are higher than with conventional infiltrations.
Post-infiltration pain is greater than with only intra-articular infiltrations and may last a few days.

PRP, platelet-rich plasma.

aforementioned limitations (Table 2). First, this administration extends the range of action of growth factors, which are gradually released from the transient fibrin scaffold generated when PRP is activated. Intra-articular infiltration makes these growth factors reach the synovial fluid, synovial membrane, and articular cartilage. Meanwhile, after the intraosseous injection, growth factors gain access to the subchondral bone and the deep layers of cartilage as a result of biological and mechanical connections between these two tissues. Second, PRP administered in an intraosseous way acts directly on the subchondral bone, whose role in the pathophysiology of OA is increasingly recognized. Lesions in the subchondral bone lead to a pathologic condition, and elevated crosstalk between the subchondral bone and the cartilage occurs, disrupting homeostasis and facilitating an inflammatory environment in the joint. The action of PRP on this structure could restore homeostatic balance, reduce the presence of inflammatory mediators, and modulate the aberrant fibroneurovascular tissue typical of joint pathologies.[7]

Both the efficacy and safety of this technique as a treatment for severe knee OA have already been tested, achieving promising results in the short-term. The patients in this pilot study showed significant improvement at 6 months after treatment and a modulation of mesenchymal stem cells (MSCs) present in the synovial fluid after the intraosseous infiltration of PRP into the femoral condyle and tibial plateau.[8] This modulatory action over the MSCs could be another key factor to address hip OA. In a recent study, Campbell et al.[9] showed that patients with advanced hip OA presented a high number of MSCs that exhibited functional as well as gene expression perturbations. Restoring the behavior of these cells could have positive effects on the development of hip OA, making the subchondral bone a key target for the treatment of this condition.[9] Therefore, the combination of intra-articular and intraosseous infiltrations of PRP would extend the distribution of PRP, improving its efficacy and acting directly on the subchondral bone, a key tissue target not only in hip OA but also in other diseases of this joint. It is still unclear if degenerative changes will be arrested or reversed, but we can affirm that this technique is a step up in the treatment of symptomatic hip OA.

References

1. Aresti N, Kassam J, Nicholas N, et al. Hip OA. *BMJ* 2016;354:i3405.
2. Xie F, Kovic B, Jin X, et al. Economic and humanistic burden of osteoarthritis: A systematic review of large sample studies. *Pharmacoeconomics* 2016;34:1087-1100.
3. Battaglia M, Guaraldi F, Vannini F, et al. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. *Orthopedics* 2013;36:e1501-e1508.
4. Sánchez M, Guadilla J, Fiz N, et al. Ultrasound-guided platelet-rich plasma injections for the treatment of OA of the hip. *Rheumatology (Oxford)* 2012;51:144-150.
5. Dallari D, Stagni C, Rani N, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip OA: A randomized controlled study. *Am J Sports Med* 2016;44:664-671.
6. Mlynarek RA, Kuhn AW, Bedi A. Platelet-rich plasma (PRP) in orthopedic sports medicine. *Am J Orthop (Belle Mead NJ)* 2016;45:290-326.
7. Sánchez M, Anitua E, Delgado D, et al. A new strategy to tackle severe knee OA: Combination of intra-articular and intraosseous injections of platelet rich plasma. *Expert Opin Biol Ther* 2016;16:627-643.
8. Sánchez M, Delgado D, Sánchez P, et al. Combination of intra-articular and intraosseous injections of platelet rich plasma for severe knee OA: A pilot study. *Biomed Res Int* 2016;2016:4868613.
9. Campbell TM, Churchman SM, Gomez A, et al. Mesenchymal stem cell alterations in bone marrow lesions in patients with hip OA. *Arthritis Rheumatol* 2016;68:1648-1659.