Current Reviews in Musculoskeletal Medicine
https://doi.org/10.1007/s12178-018-9524-x

PROTEIN-RICH PLASMA: FROM BENCH TO TREATMENT OF ARTHRITIS (S CHOATE AND J TOKISH, SECTION EDITORS)

Clinical Update: Why PRP Should Be Your First Choice for Injection Therapy in Treating Osteoarthritis of the Knee

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Abstract

Purpose of Review The purpose of this review is to update the reader on the current applications of platelet-rich plasma (PRP) in the treatment of knee osteoarthritis (KOA). This review will focus on PRP's effect on the osteoarthritic joint, how PRP compares to traditional treatments of KOA, and provide clinical feedback on the use of PRP in an orthopedic and sports medicine practice.

Recent Findings Recent research into the applications of PRP for KOA has further indicated both the efficacy and safety of PRP treatment. Although research has shown a tendency toward better efficacy at earlier stages of osteoarthritis (OA), evidence exists to indicate positive effects at all stages of OA.

Summary In summary, since KOA is an extremely prevalent condition that can be a challenge to treat, it is imperative that safe and effective nonoperative treatment methods be available to individuals that are suffering from this condition.

Keywords Knee · Osteoarthritis · PRP · Platelet-rich plasma · Intra-articular

Introduction

Osteoarthritis (OA) is the most common form of arthritis, affecting more than 30 million adults in the USA, or approximately 23% of the adult population [1, 2]. In 2013, OA was the second most expensive condition treated in US hospitals, accounting for more than US$16.5 billion spent in hospital cost [3]. The knee joint is the most common joint affected by osteoarthritis [4, 5], making osteoarthritis of the knee (KOA) a considerable health concern.

Treatment of KOA is difficult due to the avascular and aneural nature of adult knee cartilage, which results in a low regenerative capacity, and thus limited healing potential for the joint [6, 7]. The exact mechanism and pathophysiology of KOA is still unclear; however, it is clear that OA is the result of a long chain of events rather than just being "wear and tear" of the joint [7, 8]. While loss and breakdown of articular cartilage is the endpoint of this process, the entire process and progression of OA involves a combination of mechanical, cellular, and biochemical processes [9]. The joint destruction that occurs in the early stages of OA leads to an imbalance of the inflammatory mediators of the joint, resulting in further cartilage degeneration, degeneration of the extracellular matrix, systemic inflammation, chondrocyte apoptosis, osteophyte formation, and bone remodeling [9–12].

As of today, there are no definitive curative therapies for OA, meaning that treatment focuses on ways to treat patient symptoms and slow the progression of the degenerative process [13]. Thus, treatment goals for OA focus on activity modification, relieving pain and stiffness, improving joint function, improving quality of life, correcting potential deformities in the joint, and delaying or avoiding the need for total knee arthroplasty (TKA) [14–16]. While TKA is effective in treating late stage KOA, it is estimated that 10- and 20-year survivorship rates are approximately 95 and 85% [17, 18]. Furthermore, it is estimated that up to one third of TKA recipients experience chronic pain postoperatively [19, 20], resulting in a reported poor outcome rate of 20% [20]. Therefore, it is imperative that KOA be identified and treated in the stages before TKA is the only option.

This article is part of the Topical Collection on *Protein-Rich Plasma: From Bench to Treatment of Arthritis*

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Published online: 22 October 2018

The current nonpharmacological treatments for patients with symptomatic KOA begin with patient education and self-management of risk factors for OA, exercise, weight loss, physical therapy, and the use of orthotics [21, 22]. Pharmacological options include topical anti-inflammatory gels; oral non-steroid anti-inflammatory drugs (NSAIDs); oral supplements, such as glucosamine and chondroitin sulfate; and injection therapies [21, 22]. The four main injection therapies currently utilized are corticosteroids, viscosupplementation with hyaluronic acid (HA), platelet-rich plasma (PRP), and autologous mesenchymal stem cells (MSCs) [23]. For patients that do not respond to the nonpharmacological and pharmacological treatment methods, surgical options including arthroscopic surgery, osteotomy, and knee arthroplasty can be considered.

PRP is an autologous blood product that is created by first obtaining a small amount of blood through peripheral venesection, concentrating that blood sample through centrifugation, and then administering the concentrated plasma product back into the patient via an intra-articular (IA) injection [24]. The concentrated plasma product contains a high concentration of platelets (at least two times greater than whole blood), which have critical roles in maintaining tissue homeostasis and regulating the inflammation and coagulation responses of the body [25, 26], such as chondrocyte apoptosis inhibition, bone and vessel remodeling, inflammation modulation, and collagen synthesis [27]. Because of these properties, PRP has emerged as a viable treatment method for individuals suffering from KOA. The purpose of this article is to update the reader on the current information that is available regarding PRP, including the basic science involved with PRP's effect on OA, and how PRP compares to other treatment modalities.

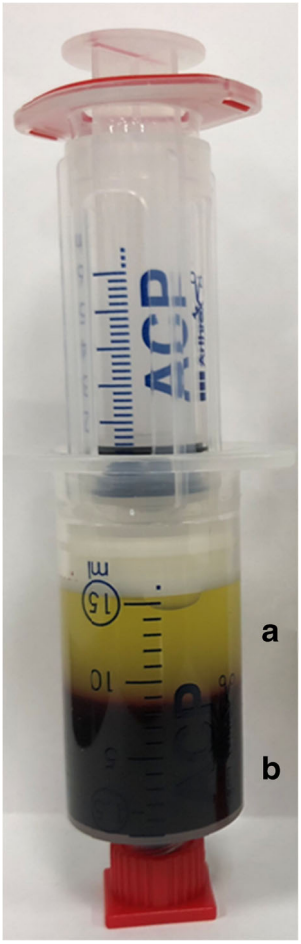

Fig. 1 The resultant product of a single spin centrifugation, with an upper plasma layer (**a**) and a lower layer (**b**) containing both leukocytes and erythrocytes

How is PRP made?

Not all PRP is the same, and preparation methods lack a standardized protocol [28]. After a blood sample is collected from the patient, that sample is run through a centrifuge, which separates the samples cellular products based on different specific gravity [29]. One primary difference in PRP systems involves this centrifugation, which can involve either one or two spins through the system. Systems utilizing one spin, such as autologous conditioned plasma (ACP) (Arthrex, Naples, Florida) and Cascade PRP (MTF Biologics, Edison, New Jersey), separate the sample into a plasma layer containing platelets and a separate layer containing red and white blood cells (Fig. 1). These one-spin systems typically result in platelet concentrations that are 1 to 3 times greater than whole blood; furthermore, the one-spin systems are efficient because they typically have short preparation times (under 10 min), which can remove the need for an anti-coagulant to be added to the preparation to prevent clotting. PRP systems that utilize two spins, like the Biomet GPS (Zimmer Biomet, Warsaw, Indiana) and MagellanPRP (Isto Biologics, Hopkinton, Massachusetts), focus on separating the blood sample into three layers: a layer with red blood cells, a buffy coat layer containing platelets and white blood cells, and a platelet depleted plasma layer. The focus of the two-spin systems is to concentrate the buffy coat layer, which contains higher platelet concentrations (> 5× whole blood) than the one-spin systems. Due to the nature of the two-spin cycle, the preparation times for these products are longer, typically 30 min or greater, often requiring the use of an anti-coagulant to prevent the sample from clotting during the preparation process.

How does PRP work?

Platelets and growth factors

Platelets are anucleated cells that are derived from megakaryocytes [30]. When platelets are activated, growth factors contained in the α-granules of the platelet respond in a localized, site specific manner [14]. This process is quick, with

almost 70% of the growth factors contained within the α-granule being secreted in the first 10 min [31]. These growth factors, along with coagulation factors, cytokines, chemokines, and other proteins stored within the platelet, have been shown to stimulate chondrocyte and chondrogenic MSC proliferation, promote chondrocyte cartilaginous matrix secretion, and diminish the catabolic effects of pro-inflammatory cytokines [32–36].

The major growth factors and growth factor families from PRP that are involved with OA treatment include tissue growth factor-β (TGF-β), insulin-like growth factor 1 (IGF-1), bone morphogenetic proteins (BMP), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF). TGF-β has been identified as one of the most important factors in cartilage regeneration because of its role in the proliferation and differentiation of chondrocytes [37, 38]. TGF-β induces chondrogenic differentiation of MSCs [39, 40] and also antagonizes the suppressive effects of IL-1, a pro-inflammatory cytokine responsible for stimulating catabolic factors, and predisposing intracapsular structures for further degradation [26, 41]. IGF-1 is an important component in cartilage processes, promoting chondrocyte mitosis and extracellular matrix synthesis [4]. BMP assists in chondrocyte migration [42], and FGF has a major role in cartilage repair [4, 32]. PDGF assists in the regeneration of articular cartilage by increasing chondrocyte proliferation and plays a role in all cells of mesenchymal origin [40, 43, 44]. VEGF effects vascular structure formation and regeneration, and has been shown to be essential in reestablishing nutrient flow [26, 45].

PRP and white blood cells

An important consideration with PRP relates to the effect of white blood cell concentration. As mentioned earlier, the products from single and double spinning procedures can vary in leukocyte concentration, typically being referred to as being leukocyte-poor (LP) or leukocyte-rich (LR). Proponents of LR-PRP argue that leukocytes are important sources of cytokines and enzymes that are important to the healing process, particularly for preventing infections [46], while others believe that the presence of leukocytes in PRP leads to an increase of pro-inflammatory cytokines and enzymes, such as matrix metalloproteinases (MMPs), which can have an antagonistic effects [44, 47–52].

A 2016 systematic review conducted by Meheux, et al. examined six level I studies involving PRP and KOA, and concluded that of the six studies examined, five displayed positive significant changes in PRP treated patients with KOA, and all utilized LP-PRP treatment [53•]. Only one study (the only study using LR-PRP) examined in the systematic review had no significant changes between PRP and the control group, which indicates that the presence of leukocytes had some effect on the study results. In support of this finding, recent evidence suggests that PRP inhibits the NF-κβ pathway, which is partly responsible in the synovial and articular cartilage inflammatory response [44, 54–57] and is triggered by pro-inflammatory cytokines. Since leukocytes are involved in the release of pro-inflammatory cytokines, it is believed the leukocytes contained in LR-PRP can cause activation of the NF-κβ pathway, possibly inhibiting the effects that PRP would have otherwise [56, 57]. It is important to note that no level I studies comparing the effects LR-PRP to LP-PRP have appeared in the literature; however, no studies describing a more beneficial effect of LR-PRP compared to LP-PRP have appeared either, to the authors' knowledge.

Other PRP influences

Along with the impact of individual growth factors, PRP has been reported to have additional effects on the osteoarthritic process. In vitro studies have shown positive effects that PRP has on chondrocyte proliferation and the enhanced production of type II collagen [36, 58–62]. PRP also appears to stimulate endogenous HA production [27] and assist with mesenchymal stem cell survival and proliferation [63, 64]. Sakata et al. found that ACP significantly stimulates cell proliferation and superficial zone protein (SZP) secretion by articular cartilage and synovium [65]. It was also found that ACP contains endogenous SZP, or lubricin, which contributes to cartilage integrity [65].

How does PRP compare in the literature?

Exercise

Exercise remains one of the first treatments recommended for the treatment of OA and has been shown to be a safe, effective method of reducing pain, and improving function in OA patients [66–68]. However, exercise has limitations as a treatment modality. One primary limitation is exercise is associated with poor compliance [69, 70]. Another limitation is exercise can be painful for individuals with OA [71, 72], and it has been shown that is can be challenging for individuals with KOA to regularly exercise [71, 73, 74]. At this current time, the authors are not aware of any research comparing exercise to intra-articular PRP injections. But, a recent randomized trial compared IA-HA injection both alone to exercise, and in combination with a personalized exercise program, and found that while both the exercise program and HA injection groups improved significantly relative to baseline measures, the combination of IA-HA injection and an exercise program provided the greatest pain relief at a 1-month follow-up [75]. This suggests that a possible synergistic relationship exists between

exercise therapy and injection therapy, and future research should be conducted both comparing PRP to exercise therapy and examining the effects of a combined IA-PRP injection and exercise therapy program.

NSAIDs

According to the 2013 AAOS evidence guidelines for knee osteoarthritis, oral NSAIDs were the only treatment modality that received a strong recommendation for treating osteoarthritis [76]. But, it is known that continued NSAID can potentially lead to severe systemic side effects that limit their usefulness of as a long-term treatment method for KOA, such as renal insufficiency, gastritis, peptic ulcer formation, and rare effects with the cardiovascular and cerebrovascular systems [21, 77–79]. The authors are only aware of one study directly comparing an oral anti-inflammatory and IA-PRP injections. Simental-Mendia, et al. compared acetaminophen use with LP-PRP injections [80]. Acetaminophen was chosen because it has a lower rate of adverse effects than NSAIDs. LP-PRP injections resulted in significantly better outcomes than did treatment with acetaminophen, with the LP-PRP group showing sustained improvement in knee function at 24 weeks post-injection [80].

Corticosteroids

Corticosteroid use continues to be one of the primary treatments of KOA [81]. A recent Cocharane review by Juni, et al. concluded that corticosteroids provided a small to moderate benefit compared with placebo 4–6 weeks after injection, a small effect can be observed at 13 weeks after injection, and no difference was noted at 26 weeks post-injection [82, 83]. Furthermore, patients should be informed that post-injection flare-ups can occur in 2–25% of patients receiving corticosteroid injections, which can last for a few days [23]. Rare soft tissue effects, such as skin depigmentation, cutaneous atrophy, and fat necrosis have also been reported in corticosteroid use [84]. In addition to the adverse effects, there is evidence that the increased usage of corticosteroid injections can lead to cartilage breakdown in a small number of patients (approximately 0.7–3.0%) [23, 85]. A recent randomized clinical trial conducted by McAlidon, et al. compared corticosteroid (triamcinolone) use to saline in patients with KOA. The authors found that the use of IA triamcinolone resulted in greater cartilage volume loss compared with saline based on MRI, along with no significant difference in knee pain severity between the two groups [86].

When compared to PRP, there again is a lack of evidence comparing corticosteroids directly with PRP. Jubert et al. compared a single LP-PRP injection to a single injection of corticosteroid in patients with late stage OA [87]. The authors concluded that PRP was effective in relieving pain and improving patient function; however, the effects of PRP were comparable to the effects of corticosteroids in patients with late stage OA. Forogh, et al. found that a single LP-PRP injection provided better pain and symptomatic relief than a single corticosteroid injection [88]. A systematic review by Meheux et al. found similar findings, noting that PRP was effective in treating OA up to 12 months post injection [53•], but echoing there is a paucity of evidence comparing PRP and corticosteroids.

Saline

While saline is typically considered a control substance to compare drug or device efficacy against, intra-articular injections of saline have recently been shown to have a significant improvement in patient reported outcomes up to 6 months after injection in patients with KOA [89, 90]. This demonstrates the significant placebo effect that can occur with injection therapies; therefore, it is crucial that potential injection therapies demonstrate consistent improved effectiveness when compared with a saline control. IA-PRP injections have consistently shown in multiple randomized studies [91, 92, 93•] to be more effective than groups injected with saline only. Patel et al. conducted the first randomized controlled trial directly comparing PRP with saline in the treatment of KOA, finding that a single injection and double injection of LP-PRP spaced 3 weeks apart of PRP were both more effective than saline in relieving the symptoms of patients with KOA [92]. In a recent FDA-sanctioned, double-blind, randomized clinical trial, Smith concluded that LP-PRP provided significant benefits for pain relief and functional improvement compared to saline that lasted up to 12 months [93•].

Hyaluronic acid

HA, an integral part of synovial fluid, assists the joint in different ways, providing lubrication, stress reduction, and substance transport across the synovium [94, 95•]. Since HA concentrations have been found to be reduced in knees with OA [94, 96], viscosupplementation with HA hopes to restore the elastic functions provided by HA back into the affected joint. But, it is important to note that unlike the autologous nature of PRP injections, HA injections are synthetically manufactured products [40, 95•]. Since HA is a commonly used injection therapy for OA patients, many studies have compared IA-PRP injections to HA viscosupplementation [46(LR),91(LR),94(LR),95•(LP),97(LP),98(LP),99(LR),100(LR),101(-LP),102(LR),103(LR),104(LP)]. The majority of these studies demonstrated superior effects of PRP when compared to HA [31, 91, 94, 95•, 97, 98, 101–104], but three studies—with two being performed by the same author and all utilizing LR-PRP [46, 100, 103]—reported comparable outcomes between HA and PRP. Cole et al. found no differences between PRP and HA in WOMAC Pain levels; however, LP-PRP was

found to be more effective than HA in other patient reported outcomes, with the PRP group displaying decreased concentrations of two pro-inflammatory cytokines at 12 weeks [95•].Of note is the 2012 study completed by Filardo et al., which despite not finding overall differences between HA and LR-PRP, indicated that PRP might be more effective in less serious cases of KOA [46], a claim that has been verified in the literature [9, 40, 102, 105, 106].

Stem cells

Stem cell treatment has received recent attention as a treatment method for KOA, with the majority of research focusing on mesenchymal stem cells (MSCs). MSCs are characterized by the fact that they are multipotent, meaning they have the ability to potentially differentiate into osteoblasts, adipocytes, chondrocytes, myoblasts, and fibroblasts depending on the method of stimulation and their differentiation potential [107]. Bone marrow aspirate concentrate (BMAC) is a popular method of delivering MSCs because it is one of the few methods allowed by the FDA to deliver stem cells due to its minimally manipulated nature [108]. MSCs are harvested from bone marrow aspiration, typically from the iliac crest, and centrifuged to isolate cellular components [28]. While stem cells are an exciting area of research, the indications in the literature for use of MSCs in the treatment of KOA is sparse [28, 107–109].

While there is some evidence in the literature of a positive effect of MSCs on KOA [110–113], there is a lack of level I evidence indicating stem cell therapy for KOA. Furthermore, a recent prospective, placebo-controlled FDA monitored study found that at 6 months follow-up, BMAC injections provided the same amount of improvement in pain and activity as saline [114•]. Stem cell harvest is also more invasive than the simple blood draw required for PRP, which could increase the likelihood of infection or complications in patients undergoing BMAC or MSC therapy. Since there is a lack of strong clinical trial evidence supporting the use of MSCs for KOA and a lack of studies directly comparing the effects of PRP and MSCs, it is not possible to recommend MSC therapy over IA-PRP injections for KOA, at this time, until further research is conducted.

Clinical use of PRP

An important component of my treatment algorithm for knee osteoarthritis is PRP treatment. I strongly believe in the importance of low white blood cell (WBC) concentration PRP based on the literature [44, 47–52, 92, 93•, 95•, 97, 98, 101, 104]. My personal preference is for the use of autologous conditioned plasma (ACP) (Arthrex, Inc. Naples, Florida) for several reasons. First, it has a very low WBC concentration. Secondly, it is a single-spin system and laboratory studies

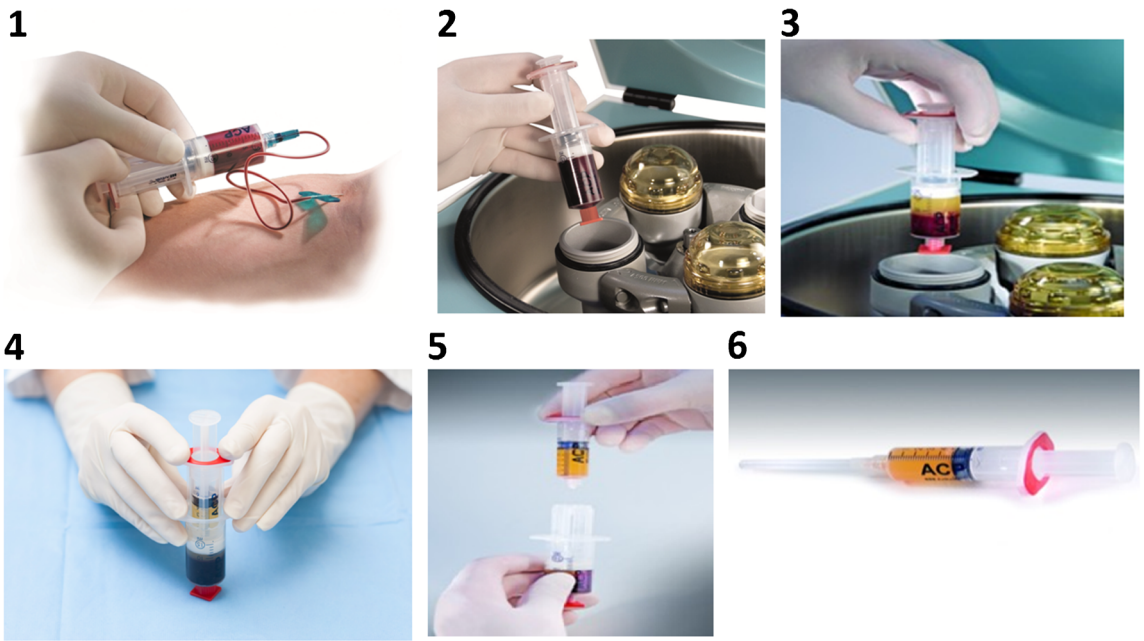

Fig. 2 From harvest to finished product. (1) A small blood sample (15 cc) is acquired through venipuncture; (2) the collected sample is centrifuged (5 min; 5000 rpm); (3) after the centrifugation is complete, the sample is ready to be separated; (4) using the double-syringe system, the plasma layer is separated from the lower layer containing leukocytes and erythrocytes; (5) the inner syringe, now containing the ACP, is separated from the outside syringe, which contains the discarded leukocytes and erythrocytes; (6) once a needle is attached, the ACP is ready to be injected

have shown compared to a double spin system, it reduces cytokines and may stimulate HA production [27] and increase Lubricin [65]. It is very convenient and efficient to use in the outpatient office setting, as only 15 cc of blood is drawn, and the same "double" syringe done for the blood draw is used for centrifugation, as well as the subsequent PRP extraction and injection (Fig. 2). So, it is a completely self-contained system. Centrifugation is only a 5-min spin which saves a lot of time. Typical ACP volume attained to be injected is 4 to 6.5 cc. Plus, an anti-coagulant-like ACD-A is not necessary with the ACP injection, which I believe helps to minimize any potential joint reaction from the injection as ACD-A has a low pH. I inject after a sterile prep from a lateral parapatellar approach. I do not believe ultrasound is necessary to inject the knee joint in most cases. Typical overall time of treatment with ACP for one of my patients from when they first arrive in an exam room and have their blood drawn and spun, and then their knee injected, is routinely under 15 min.

Based on the results of a randomized controlled trial, my protocol is three ACP injections 1 week apart [93•]. I recommend icing after the injection and tell patients not to push it from the exercise standpoint until a week after the third injection. In my experience based on feedback and the need for repeat injections, patients have good pain relief for at least 6 months and commonly, for a year or longer following the three-injection regimen. One issue is whether three ACP injections are necessary. I have had instances where patients have only had two of the three injections and reported good pain relief and function. So, this is an issue that needs future study. Maybe patients with less severe KOA such as KL grade 1 and 2 need only one or two injections, and the more severe KL grades of 3 and 4 need three injections. Or, maybe, the more severe KOA patients need four, five, or six injections to get maximal relief—another area of potential study.

I firmly believe biologic injection treatment for knee osteoarthritis is both safe and efficacious. The major challenge going forward is obtaining approval for this important treatment for our patients from major insurance companies and the government (CMS). It bothers me that the lack of regulation has led to many providers charging high fees to patients for biologic injections, which is all "out-of-pocket" [115]. There are obviously some costs involved with equipment and physician time for the procedure, but some clinics have extremely high fees. Furthermore, false advertising is prevalent under the guise of "regenerative medicine." Biologic injections like PRP or stem cells obviously does not "cure" arthritis, but unsuspecting patients in pain are sometimes very vulnerable to believing false claims. There is very strong clinical evidence that low WBC PRP injections are clinically effective for treatment of knee osteoarthritis, and now that message must be communicated effectively to insurance providers, as I believe once insurance coverage is in place than the marketplace of exorbitant and unreasonable charges for this treatment will go away.

Conclusions

Moving forward, it is imperative that future clinical research be conducted in a more standardized manner, ensuring that reproducible methodology is available and minimizing study-to-study variability. This includes PRP preparation methods (centrifugation times and speeds, harvest methodology, systems being used); PRP composition (platelet concentrations, activation agents, white blood cell concentrations, growth factor and cytokine concentrations); PRP injection protocols (single versus multiple injections); sufficient clinical follow-up (a minimum of 6 months); and strict inclusion/exclusion criteria [116•]. These steps will allow future evidence from well-structured clinical trials to be more comparable with one another, furthering our understanding of the effects PRP has on the osteoarthritic process.

Compliance with Ethical Standards

Conflict of Interest Dr. Smith is a consultant for Arthrex and receives research support from them.

Dr. Cook has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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