

Is platelet-rich plasma right for your patient?

Many pro athletes claim that platelet-rich plasma has improved their performance and saved their careers. But is it right for your patients? And if so, which ones?

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PRACTICE RECOMMENDATIONS

› *Inform patients with knee osteoarthritis that although evidence is limited, platelet-rich plasma (PRP) injections may improve pain and function in the short-term. (B)*

› *Advise patients with elbow epicondylitis that PRP injections may improve pain and function slightly more than corticosteroid injections in the short-term. (B)*

› *Counsel patients that PRP has minimal risks; however, larger studies are needed to more fully assess whether harms exist. (B)*

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▶ Ms. T is an otherwise healthy 76 year old with a history of severe osteoarthritis (OA) in her right knee. She has participated in multiple rounds of physical therapy (PT) over the last 3 years. During the past year, she received 2 intra-articular corticosteroid injections, each of which provided only 3 to 4 weeks of pain relief, and one hyaluronic acid (HA) injection, which provided no benefit whatsoever.

Today, she describes her right knee pain as an 8 out of 10 and is frustrated by her lack of symptom relief. She was planning to have a total knee replacement and is a good surgical candidate, but recently found an article regarding platelet-rich plasma (PRP) injections for knee OA. She wants your opinion as to whether she should try this approach or proceed with surgery.

CASE 2 ▶ Mr. H is a 44-year-old, right-handed dentist who has been suffering from right lateral epicondylitis for the past year. Although he has undergone PT and has been performing exercises at home since his symptoms began, he has not noticed a significant improvement. In the last 5 months, he has been out of work a total of 8 weeks due to the pain. He received one corticosteroid injection last month, which provided no improvement in symptoms. He is not interested in surgery, as he does not want to be out of work for a prolonged period of time.

He reports that one of his friends recently received a PRP injection for lateral epicondylitis and now feels great. He is aware that PRP injections are not covered by his health insurance and says he is willing to pay out of pocket if the treatment works. He wants to know if you recommend this course of action for his elbow pain.

How would you counsel each of these patients about the use of PRP injections for pain relief from their respective orthopedic conditions?

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Platelet-rich plasma is thought to tip the body's response in favor of regeneration over destruction.

Musculoskeletal symptoms account for 10% to 28% of patients' complaints to primary care physicians annually.¹ Treatment of both chronic tendinopathies and knee OA—2 of the most common causes of these complaints—typically follows a stepwise approach, beginning with anti-inflammatory and pain medications in addition to PT. Patients who fail to respond to these interventions are often treated with corticosteroid injections, and, in the case of knee OA, viscosupplementation (ie, HA injections) and braces. If these therapies fail, patients are often forced to choose between an invasive surgical procedure or continued pain and limited function.

A number of physicians specializing in musculoskeletal medicine have turned to prolotherapy—specifically, dextrose prolotherapy (see “Prolotherapy: Can it help your patient?” *J Fam Pract.* 2015;64:763-768) and platelet-rich plasma (PRP) therapy—as an alternative treatment for chronic musculoskeletal conditions.

PRP has been used to enhance surgical healing and to treat muscle strains and chondropathies. It drew a great deal of attention in the media when it was used by such high-profile professional athletes as Tiger Woods and Kobe Bryant.

Although PRP therapy is not commonly reimbursed by health insurance companies because of a lack of large, definitive studies supporting its effectiveness, patients are paying anywhere from a few hundred to a few thousand dollars out of pocket for it. They're doing so in the hope that it will treat their chronic musculoskeletal disorders or at least delay surgical procedures.

But what can these patients reasonably expect from this therapy?

The following review of the evidence for PRP in the treatment of knee OA and tendinopathies (including elbow epicondylitis, patellar tendinitis, and Achilles tendinitis) will help you counsel patients on its appropriate use.

What is PRP?

PRP is defined as a sample of autologous blood with concentrations of platelets above

baseline values.² It is made through a one- or 2-stage centrifugation process in which the liquid and solid components of whole blood are separated, and then the liquid components are further separated into portions that are platelet-rich and platelet-poor.

Significant variability in preparation methods exists, resulting in more than 40 different products.² Some methods centrifuge only once, creating plasma that is separated from red and white blood cells, but without a huge shift in the concentration of platelets; some include white blood cells in the final preparation; and most have differing concentrations of platelets and various growth factors in the end product. Researchers have attempted to classify the various preparations by platelet concentration, inclusion or exclusion of white blood cells, and fibrin content, but no validated system yet exists. Thus, consistency in preparations is lacking.^{3,4}

PRP is rich not only in platelets, but also in a multitude of other growth factors. It is thought to improve healing by enhancing the body's natural regenerative processes at the tissue level. In OA, for example, a complex balance of destructive and reparative processes is at play; PRP is thought to tip the body's response in favor of regeneration over destruction. Similarly, chronic tendinopathy involves a process of destruction, reaction, healing, and degeneration; intervening at the correct point in this pathway with a boost to healing may help the body repair an otherwise diseased tendon.³

What does the evidence show?

Overall, basic science and preclinical research support “the promise” of PRP (strength of recommendation [SOR]: **A**).⁵ However, patient-centered evidence is lacking, and tremendous variability exists between studies, not only in terms of PRP preparation, but also with regard to:

- **Protocol**—Was ultrasound guidance used? Did the injection include needling of the tendon? What post-injection rehabilitation was followed?
- **Patient population**—What treatments were tried in the past? How chronic or severe was the problem?

- **Study design**—What was the comparison group? How were pain and function measured? Most studies have been small in size and have included various treatment modalities in addition to the PRP injection (most often PT).

Knee OA: PRP may provide short-term benefit, especially in younger patients

Researchers have conducted a number of studies evaluating PRP for knee OA.⁶⁻¹² Most have compared PRP to HA—another intra-articular injection that is plagued by mixed, limited, and poor-quality evidence. These trials have had varied results and do not consistently support PRP as superior to HA.

The most well-designed study to date demonstrated that PRP was superior to saline and as effective as HA.¹¹ In addition, the researchers found that a series of 3 PRP injections was superior to 3 injections of HA or only one injection of PRP.

One small randomized controlled trial (RCT) compared PRP injections to saline and found that PRP improved pain and function better than placebo at 6 weeks, 3 months, and 6 months; results appeared to deteriorate after that time period.⁶ Also, the findings suggested that PRP delivered the strongest benefit in younger patients who had less advanced OA.

In addition, a recent systematic review found short-term improvements in functional outcomes in patients treated with PRP injections vs those treated with HA injections and those treated with placebo.¹²

But before experts can make any conclusive recommendations regarding the use of PRP for knee OA, standardized studies with larger numbers of participants and rigorous methodology must be designed. Notably, no evidence exists of significant harm resulting from PRP injection for knee OA. Therefore, given the mixed evidence in terms of efficacy, there may be a potential benefit to treatment with little negative consequence.

■ **In 2013, the American Academy of Orthopaedic Surgeons (AAOS) stated** that they were unable to recommend for or against PRP injection for patients with symptomatic OA of the knee because the evidence was in-

conclusive.¹³ At the same time, the AAOS was unable to recommend for or against corticosteroid injections, manual therapy, or bracing for knee OA, and recommended against HA injections.¹³ Recently, however, the American Medical Society for Sports Medicine (AMSSM) recommended that HA be used in appropriate patients with knee OA.¹⁴

■ **Such disagreement indicates that evidence is lacking for many modalities** employed in the management of knee OA, including the injection of corticosteroids, which is a frequent and generally accepted treatment. Compounding matters is that many of the original studies testing the efficacy of PRP injection in knee OA used HA injections as the comparison, and there is no agreement between AAOS and AMSSM as to its usefulness. Thus, the validity of using HA as a control is suspect.

Tendinopathies: PRP may have benefit, but more research is needed

A number of meta-analyses and systematic review articles have combined the results of studies involving PRP treatment for various tendinopathies.^{3,15-17} While most found that PRP may have a benefit (although not long-lasting) and may be of use in attempts to avoid surgery or to return to a desired activity, all reported that more rigorous studies with standardized methodologies must be conducted before PRP can be conclusively recommended for any anatomic site.

■ **Elbow epicondylitis (tennis elbow).** The majority of tendinopathy studies have examined the effect of PRP on tennis elbow, although given the small study numbers (N=20-100), high risks of bias, and very different comparison groups, the data are extremely limited. Of the 4 randomized studies,¹⁸⁻²¹ 2 compared different PRP preparations to whole blood,^{18,20} one compared PRP to both saline and corticosteroid,¹⁹ and one compared PRP to corticosteroid alone.²¹

The studies comparing PRP to whole blood found similar outcomes at most time points.^{18,20} These studies were of extremely poor quality, and other review articles have defined whole blood as a type of PRP, so this comparison was somewhat inappropriate. One recently published meta-analysis,



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➤ There is no evidence of significant harms associated with platelet-rich plasma treatment, but studies have lacked the power to detect rare but serious problems.

which included 10 studies comparing either PRP or whole blood to corticosteroid, found that PRP improved pain more than a corticosteroid.²²

The one study that included a comparison of PRP to placebo (saline) suffered from a high dropout rate, and the authors were not able to analyze the primary outcome data. At 3 months, the participants remaining in each group (PRP, saline, or corticosteroid) had similar pain and disability scores.¹⁹ Although the steroid group had improved from baseline at one month, there was no difference between the steroid group and placebo group at 3 months. The PRP group did not differ from the placebo group at any time point.

The study comparing PRP to corticosteroid alone found that PRP's effects on pain and function exceeded those of the steroid. Specifically, the steroid group initially improved and then worsened, ending the study near their baseline pain and function scores.²¹ The PRP group, on the other hand, showed slow improvement throughout, ending the study with less pain and disability than when they started.

■ **Patellar tendinitis (jumper's knee).** The majority of studies examining the effect of PRP on patellar tendinitis are non-randomized, non-comparative studies. Of the 2 small RCTs that were conducted, one compared PRP to extracorporeal shock-wave therapy (ESWT),²³ and the other to dry needling.²⁴

In the ESWT study, there was a slight improvement in pain and function in the PRP group relative to the ESWT group at 6 and 12 months. In the other study, although the PRP group showed an improvement in recovery at 12 weeks relative to the dry needling group, there was no difference between such outcomes as pain and activity in the 2 groups at 26 weeks.

Worth noting here is that like the studies done on OA patients, the research involving patellar tendinitis also used comparative interventions (ESWT and dry needling) that lack high-quality evidence for their use. So whether these were appropriate comparisons is debatable.

■ **Achilles tendinitis.** Only one RCT (N=54) has evaluated PRP for the treatment

of Achilles tendinitis.²⁵ This study, which compared PRP to saline, excluded patients who had previously completed a course of PT, yet both study groups participated in PT during the study. Although the trial found no difference between groups at any time point (both showed improvement), it was underpowered to detect any difference (positive or negative) between groups, given that most participants likely would have improved with PT anyway.²⁶

PRP has few harms or adverse effects

Most individual studies involving PRP have not reported on harms or side effects; the studies that have reported on them have generally found low rates (2%-5%) of only local, short-term adverse effects.¹⁵ One review article did find that increasing the number of PRP injections increased the rate of adverse effects; however, those effects still appeared to be mild and time-limited.¹⁰

One study reported that 33% (17/51) of patients experienced systemic adverse effects including syncope, dizziness, and nausea at the time of their PRP injection.⁶ Overall, there is no evidence of significant harms associated with PRP treatment, but available studies have lacked the power to detect rare but serious problems.

Looking to the future:

Additional considerations

In order to properly evaluate this potentially promising method of care, future studies need to include appropriately chosen controls, specifically defined formulations of PRP, standardized protocols for the injection of PRP, standardized post-injection PT regimens, and patient populations that are clearly defined in terms of severity and chronicity of disease. Furthermore, studies must be rigorously designed in terms of randomization, blinding, and analysis. (Many studies done to date did not use an intention-to-treat protocol, for example). Higher-quality studies with larger numbers of participants are the only way to determine whether PRP is worth all the "buzz."

We should keep in mind, too, that the

evidence for many of the other treatment options for both tendinopathy and knee OA are similarly problematic, and these modalities are even more widely used than PRP. Given the systemic problems associated with nonsteroidal anti-inflammatory drugs, concerns about possible tendon rupture with corticosteroid injections, and the time and compliance issues associated with PT, PRP may be a safer alternative to more traditional treatments.

An off-label use. PRP does not pass through the standard regulatory pathway of the US Food and Drug Administration (FDA). As a blood product, PRP falls under the regulatory purview of the FDA's Center for Biologics Evaluation and Research, which has approved PRP only for use in the operative setting to enhance bone graft handling properties.²⁷ Therefore, office-based PRP injections are an off-label use of the treatment.

CASE 1 ▶ You explain to Ms. T that PRP injections are not covered by insurance and that there is not a significant amount of evidence to indicate that an injection would appreciably improve her pain. She decides to proceed with a knee replacement and not to pursue a PRP injection.

CASE 2 ▶ Given the time that Mr. H has invested in traditional conservative management strategies, his time away from work, and that he is not concerned with the out-of-pocket cost associated with PRP, you explain to him that there is some limited evidence that PRP might improve his symptoms. He decides that he would rather try a PRP injection than pursue surgery. **JFP**

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