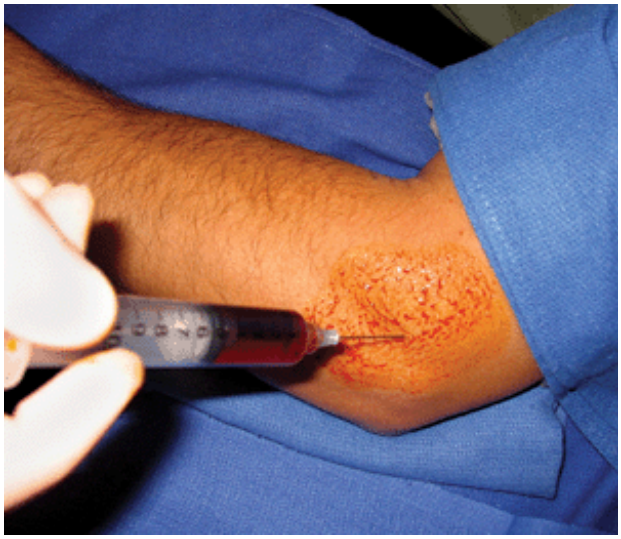
AAOS Now

Platelet-rich plasma: Clarifying the issues

Recently, *AAOS Now* convened a panel of experts to discuss what may be the hottest topic in orthopaedics this year—platelet-rich plasma (PRP). Joining moderator **Jo A. Hannafin, MD, PhD,** were **Steven P. Arnoczky, DVM; Freddie H. Fu, MD;** and **Allan K. Mishra, MD.**



An injection of PRP is used to treat lateral epicondylitis in the left elbow. Courtesy of Allan K. Mishra, MD

Dr. Hannafin: I did a Google search and found more than 400,000 citations for PRP treatment, including YouTube videos on how the procedure is performed. Clearly, patients, physicians, and scientists are interested in the use of PRP. What conditions is PRP being used for?

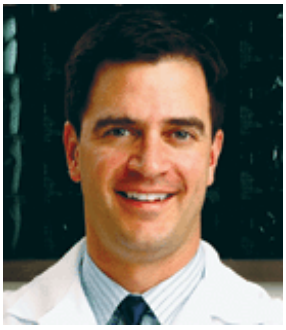
Dr. Mishra: I use it almost exclusively in treating tendinopathy, particularly chronic tendinopathy that has failed to respond to other treatment modalities. That would include conditions such as chronic, recalcitrant lateral epicondylitis, patellar tendinopathy, and Achilles tendinopathy. I think the data—and the work that I have been doing for almost a decade now—provide the greatest support for its use in that area.

Dr. Fu: I see many people are using PRP for acute injuries as well, which concerns me. I'll go to a meeting and somebody will report on a new indication for using PRP. But this is a controversial situation. People can work on it on a basic science level and really do some quality studies. But to extend its use to many other conditions does not make much common sense at this time.

Jo A. Hannafin, MD, PhD

Steven P. Arnoczky, DVM

Freddie H. Fu, MD



Allan K. Mishra, MD

Dr. Hannafin: Do you have any experience using PRP for muscle injuries?

Dr. Fu: I have not personally used it for muscle injury, although some of my partners have. I do follow the research being done in muscle injury. From the work of Johnny Huard, PhD, for example, we know that using platelets in muscle injury is tricky. Although platelets are regenerative, they contain growth factors that, when applied at different times in the healing process, can actually cause fibrosis. In any condition, we must understand the mechanism of healing and of the injury cycle. We want to minimize the bad side effects of treatment and get a better healing process for muscle injury.

Dr. Arnoczky: Not all PRP preparations are similar. Several different forms of PRP or PRP-derived products have been used in human medicine. Besides the liquid or gel form of PRP, a platelet-rich fibrin matrix is currently being used in meniscus repair, rotator cuff repair, and anterior cruciate ligament reconstruction. The presence or absence of red blood cells and white blood cells as well as the addition of thrombin or calcium chloride further delineate the various preparations. We must be careful to compare 'apples to apples' when we speak of the outcomes using PRP. We must acknowledge that not all PRPs are alike and thus the success or failure of one PRP preparation does not necessarily translate to all PRPs.

Dr. Mishra: PRP has been discussed in both the medical and lay literature as something that isn't heterogeneous, and that's not the case. I developed a classification system (in press, *Current Pharmaceutical Biotechnology* 2010) so we can compare types of PRP. When we talk about PRP, we need to discuss three issues: the concentration of the platelets over baseline, the presence of white blood cells in the formulation, and the need to activate it prior to using it.

I'm not sure that asking whether PRP works, where it works, and when should we use it are the appropriate questions. We need to look at the formulations that exist and how they can be best applied. I predict that we will find that specific types of PRP work better for specific indications. For example, the PRP formulation that is better for acute muscle injuries may be very different from the one that works with chronic tendinopathy because these are clearly different pathologies.

Dr. Fu: All these factors are already within our bodies during the natural healing response, which has developed over millions of years of evolution. I really want to know how we can improve our own biologic response, especially in an acute injury setting or during healing.

Dr. Arnoczky: I agree wholeheartedly. I haven't seen any basic science or clinical literature showing that a healthy wound in a normal individual with healthy tissues heals any faster when any type of biologic adjunct is applied, whether PRP or individual growth factors. Other things may happen—it may be stronger if we add collagen—but it really doesn't heal any faster.

So, I think the biologically compromised tissues that Dr. Mishra talked about are the ones that may benefit from the addition of growth factors or other cytokines present in PRP. We tend to focus on growth factors and their benefits, but a whole plethora of bioactive molecules are present not only in the alpha granules of platelets but also in the plasma component of PRP. In all of these different systems, the most consistent thing is the plasma, which contains important proteins for wound healing, as well as the fibrinogen and fibrin scaffold that is generated when the platelets are activated with thrombin or calcium chloride.

Dr. Hannafin: Do we have a basic science explanation of why PRP works or doesn't work in different sites or with different formations?

Dr. Arnoczky: We don't know precisely why it works; there may be advantages for having white blood cells in certain indications or the plasma component and the growth factor component in other indications. That's a major variability, as is the variation in platelet content

of the final PRP product. PRP is not a precisely controlled product. Independent studies are showing that even when using a single technique, it's almost impossible to replicate a consistent level of platelet concentration.

We also have to be careful in defining outcome variables. We are looking at a biologic adjunct, which may have an early effect. Therefore, if we measure an outcome variable such as function at one year, it may not be different because the beneficial effect of PRP may occur early in the healing process. Conversely, the beneficial effect of PRP may occur later with improved tissue quality so the incidence of repeat injuries (such as the retear rate in rotator cuff repair) may be less.

I also think that clinical studies need to be more nuanced and appropriately powered (statistically). Many of the studies in the current literature are underpowered. Some studies have shown no difference in outcomes when using PRP. I think this is because they are looking for a "home run." They are looking for a huge (ie, 25 percent) improvement in some variable.

Dr. Mishra: I have been working on a prospective, double-blind, randomized trial of 230 patients with lateral epicondylar tendinopathy under the direction of the U.S. Food and Drug Administration. We are likely to finish enrolling patients this year. This study of PRP versus a saline control will provide some evidence of its value in treating that particular problem at that particular stage. But just because PRP works in tennis elbow doesn't necessarily mean it will work in acute muscle injury; they are just dramatically different problems.

Dr. Fu: The outcome evaluation of these conditions is not easy.

Dr. Mishra: I agree, and I am using ultrasound as an objective measurement of the size of the lesion, whether it's in the patellar tendon, the Achilles tendon, or at the proximal lateral epicondylar insertion point. As we move forward, we will need not only validated outcome questionnaires and pain measurements, but also objective measurements such as size of the lesion or the thickness of the tendon as measured by ultrasound.

Dr. Hannafin: What current, published research supports the use of PRP and for what conditions? What are your clinical indications for use of PRP and where?

Dr. Fu: I know of five level I studies and several trials to show the use of PRP in vivo. Two show no differences, two show better healing with PRP, and one shows higher benefit of an alternate treatment. There are many case reports and lower level studies, but not much high-quality scientific work.

Dr. Mishra: I think that Taco Gosens' study of PRP versus a cortisone injection is pretty definitive. It shows that PRP is better than cortisone, which may or may not be the best control group. But 93 percent of orthopaedic surgeons have treated tennis elbow with cortisone, and I think it may be reasonable for patients to be offered PRP instead based on that level I evidence.

I also agree that practitioners who are using PRP should be obligated to evaluate the results as

objectively as possible and present or publish them. As Dr. Fu said, the body has a fair amount of power to heal itself, and physicians are trying to better understand how to concentrate and apply that power appropriately.

Dr. Arnoczky: Basic science and preclinical research certainly would support the *promise* of PRP to have a beneficial effect in connective tissue repair. Many studies have shown that adding growth factors—either as a cocktail or in PRP—results in increased cellular proliferation, increased matrix synthesis, and increased extra matrix properties. Some animal studies have looked at the effect of PRP or PRP types of products on muscle contusions and have shown decreased fibrosis and what appears to be better healing from the satellite cells proliferating.

Dr. Fu: I agree. Basic science studies show a positive effect. The question is: How does it translate to animals, and ultimately, to the treatment of patients? This is hard to know.

Dr. Mishra: As we move forward, it may be best to look into those preclinical environments to learn some of the mechanisms that are going on and then proactively decide where to apply PRP. Right now, we are doing it the other way around—using PRP everywhere and trying to understand how it works.

Dr. Arnoczky: I think enough substantive data existed to justify the use of PRP before we had clinical models. However, if we are ever going to completely unravel the potential benefits of PRP in treating a given pathology, we may have to focus on one or two specific PRP preparations and look at them in a prospective, randomized way. Even within tendinopathy, the pathology is so varied that it's a very heterogeneous population. We may never know what's going on at the cellular level until we have more sophisticated techniques (ie, imaging) than we do now.

Dr. Fu: What about using PRP in a model that allows us to measure healing with magnetic resonance imaging (MRI) and correlate this to histology, biomechanics, and basic science studies? This has not been done and needs to be addressed.

Dr. Arnoczky: Whether the patient does better is probably going to depend on the extent to which the natural history of the repair response of a given pathology can be altered by PRP.

Dr. Fu: I agree; we have to look at the cost-effectiveness of this procedure, particularly in the long run.

Dr. Mishra: We may be interested in creating a perfect biologic treatment, but that cannot be done in a vacuum. As we move forward to cover more patients and at less expense, new therapies not only have to be better, they have to be less expensive than the status quo. You have to test new therapies against a standard and show which is better and more cost effective.

Dr. Hannafin: It appears that we have some consensus among the group that PRP therapy may be beneficial for the treatment of certain specific conditions such as lateral epicondylitis. In other areas, we don't have strong data to support the use of PRP. What is the downside of PRP? Is there potential risk to these injections?

Dr. Fu: Chronic conditions may not have a big downside risk, but I don't think you can use PRP in acute cases—such as ankle sprains or medial collateral ligament injuries. It may not be beneficial with effective healing, and if people go back to play early, they can potentially hurt themselves. Mostly I worry that the diagnosis is not being made properly, as with a stress test or an MRI to identify a high ankle sprain, for example. PRP is now being used for pain control and faster healing. Potentially this could lead to further injury to the patient, so this is the downside I see.

Dr. Mishra: I agree. PRP therapy needs to be defined by specific injury or tissue type; it's not going to work for everything. We do ourselves a disservice by not being scientific about how we approach this.

I've been using PRP for many years, but still do not use it widely for a variety of different indications. A prospective trial published last year from the University of Bologna (Italy) found that a PRP injection was safe and potentially reduced pain and improved knee function in patients with osteoarthritis of the knee. The formulation was specific and reported in the study so that the data may be able to be replicated.

Dr. Arnoczky: Other European studies have looked at autologous conditioned serum, not PRP. The platelets are lysed and the fibrinogen is removed to leave just the serum; this has shown good results when injected into the knee.

From a basic science viewpoint, at the tissue level, PRP has no downside. It provides the same molecules that occur following hemorrhage in a tissue. This, coupled with the autologous nature of PRP would suggest that it is safe.

Dr. Fu: Dr. Huard's studies on muscle healing showed that the growth factor TGF-ß actually caused fibrosis. Fibrosis was not a big issue with cavemen, but today's athletes need good muscle to function at a high level. So this particular growth factor may cause an effect we don't want to see. We need to understand the mechanism of healing and address the process with an appropriate biologic treatment before we can guide patients in a beneficial direction.

Dr. Mishra: We have found some evidence that PRP, in a certain in vitro cell line under stress, reduces apoptosis, and we are sifting through a fair amount of micro array data. Perhaps the AAOS or the Orthopaedic Research Society should assemble a group that would agree upon certain specific research goals, because collectively we might be better able to answer some of these questions.

Dr. Fu: I agree. I went to the PRP expert at the dental school at the University of Pittsburgh and he is not sure how it really works. Dentists are 15 years ahead of orthopaedists in the use of PRP and they should have some definitive answers, but the dental literature shows varying results of efficacy. We need to work together and put this at a high level.

Dr. Hannafin: In the New York metropolitan area, the fees for PRP injections vary

widely, and most are not covered by health insurance. What is the range of cost for PRP injections in your area and are those injections reimbursed by insurance?

Dr. Mishra: Some of the kits are more sophisticated than others and some people are recommending more injections than others. I'm in the West where charges for PRP therapy range from $1,000 to $2,000. I don't know of any specific insurance coverage right now.

Dr. Hannafin: In closing, do you have any overall comments on PRP and the status of its use?

Dr. Arnoczky: We really have to understand how PRP can add to the healing response as an adjunct or a stimulant in different pathologies. Once we understand what these mechanisms are, we would have a pretty good idea of where it can be most beneficial.

Dr. Fu: I think PRP is being market-driven. We have to take it back into our own hands. We need basic science and high-level clinical studies so that one day we can tell everybody how it should be used.

Dr. Mishra: I predict that we are going to find newer and more precise formulations of PRP that make sense for specific indications. The indications will narrow but they will be more definitive. We also have an obligation beyond our own specialty because PRP may work in areas beyond orthopaedics. If we can collectively better understand how it works, we may be able to contribute not just to our own orthopaedic patients but to others as well.

Disclosure information: Dr. Hannafin—no conflicts; Dr. Arnoczky—Musculoskeletal Transplant Foundation; Wright Medical Technology, Inc; Regeneration Technologies, Inc.; Smith & Nephew; NovaLign Orthopaedics, Inc.; Active Implants Corp.; Journal of Bone and Joint Surgery-American; Osteoarthritis and Cartilage; Journal of Orthopaedic Research; Orthopaedics Today; American Journal of Sports Medicine; Scandinavian Journal of Medicine and Science in Sports; Journal of Knee Surgery; *Dr. Fu—Arthrocare; Stryker; Smith & Nephew; Saunders/Mosby-Elsevier; Orthopaedic Research and Education Foundation; American Orthopaedic Society for Sports Medicine; International Society of Arthroscopy; Dr. Mishra—Biomet, Bioparadox.*

AAOS *Now*
September 2010 Issue
http://www.aaos.org/news/aaosnow/sep10/clinical1.asp

9400 West Higgins Road Rosemont, Illinois 60018 Phone 847.823.7186 Fax 847.823.8125