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Platelet-rich plasma: More than a last resort?

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Findings from studies of PRP can be conflicting and confusing, but lower extremity practitioners remain cautiously optimistic about the trendy treatment's clinical potential to accelerate healing of soft tissues, bone, and diabetic wounds.

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by Cary Groner

Recent clinical trials reporting that platelet-rich plasma (PRP) therapy may be less effective than previously believed have stoked the debate about this futuristic healing technique.

Whereas earlier, positive studies have been criticized for weaknesses that include small sample sizes and a lack of controls, newer and more critical research turns out to have Achilles heels of its own. For example, a 2010 *Journal of the American Medical Association* paper reporting no significant difference between PRP and saline injection in patients with Achilles tendinopathy included variables such as eccentric exercises—which have significant curative powers by themselves—and multiple needle perforations in both treatment and control groups.[1] The latter approach, percutaneous needle tenotomy, has been shown to stimulate the inflammatory response that jump-starts healing regardless of whether anything is injected into the tissue.[2] In the *JAMA* study, perhaps not surprisingly, both groups got better, though PRP offered no significant advantage over saline.

By contrast, research published in the *American Journal of Sports Medicine* in 2007 followed 12 athletes following surgery for complete Achilles tendon tears. The six who received PRP as part of the repair recovered their range of motion earlier (seven weeks vs 11 weeks), took less time to resume gentle running (11 weeks vs 18 weeks), and returned to training activities at an average of 14 weeks, compared to 21 weeks for those who had surgery without PRP.[3]

In the face of confusing reports, clinicians are falling back on their own experience to make treatment decisions. Nevertheless, as research continues and anecdotal evidence accumulates, a vision of PRP's place in evolving therapeutic approaches is emerging from the murk.

"I feel guarded optimism," said Sean Grambart, DPM, an instructor at the University of Illinois School of Medicine and a foot and ankle surgeon at the Carle Clinic in Champaign, IL. "As we look at the literature from the past couple of years, we see that PRP may not be as effective as we'd hoped. But as a last-ditch effort to avoid surgery in Achilles tendinopathy, for example, it's cost-effective and it makes sense. You can look at the studies, but you have to take into account what you're seeing clinically, and I'm seeing people get better."

Hastening diabetic wound healing

Platelet-rich plasma therapy appears to be effective to speed healing in diabetic foot ulcers and similar wounds, research shows.

In a 2010 case study from the Southern Arizona Limb Salvage Alliance (SALSA) at the University of Arizona College of Medicine in Tucson, a 49-year-old man with a history of diabetes and a deep, nonhealing plantar hallux wound received PRP and a first metatarsophalangeal joint arthroplasty, then healed uneventfully at seven weeks.[1]

Other studies[2-4] have reported positive outcomes associated with the use of PRP gel on recalcitrant diabetic foot ulcers. In a presentation at the March 2010 Diabetic Foot Global Conference (DF-Con), clinicians at the Carl T. Hayden Veterans Administration hospital in Phoenix used PRP gel on 14 large, recalcitrant wounds in 10 diabetes patients. Of those, 86% responded positively, showing an average 75% decrease in volume and a 67% reduced area (see "Large, stubborn foot wounds respond to treatment with platelet rich plasma," April 2010, page 11).[2]

"We're starting to see more of the promise of things like processed plasma, as well as pluripotent or multipotent cells, in and around the wound," said SALSA director David Armstrong, DPM, MD, PhD. "As we get better in diagnostics and theranostics, we're going to be cutting back farther and farther until we get to healthier tissue. The great promise may not be on the wound; it may be around the wound, where the tissue may be more metabolically receptive."

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How it works

PRP has been used for years in maxillofacial and orthopedic surgery.[4] The substance itself is supplied by the patient; vendors sell the tools and chemicals of collection, concentration, and activation. Blood is drawn and centrifuged, then PRP is collected and treated before being injected into the injured area, usually with ultrasound guidance.

It works, at least theoretically, because platelets and blood plasma contain a variety of polypeptide growth factors important for regulating the growth and development of a variety of tissues.[5,6] These growth factors include platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor 1(IGF-1), and various cytokines.

The results of processing yield PRP with varying degrees of platelet concentration, roughly two-and-a-half to nine times baseline levels.[7] It may, moreover, be relatively leukocyte rich or poor. Depending on the projected use, it also may be activated with thrombin, calcium, or calcium chloride; or it may not have an added activator at all (in such cases, it is activated by the collagen in the patient's tissue after injection).

Clinicians express consternation at the research partly because it has been conducted with all manner of different PRP preparations, making results difficult to compare. For example, some suggest that relatively lower concentrations of platelets, in the 2.5-times normal range, may be more effective than higher concentrations.[8] But differing levels of growth factor aren't just byproducts of different concentration methods; they also occur naturally due to patient heterogeneity.

"You may have blood draws from ten different people and come up with totally different concentrations of growth factor," Grambart said.

Kimberly Harmon, MD, a clinical professor in the departments of family medicine and orthopedics at the University of Washington, added that there's significant variety even within individuals.

"Platelet counts vary over time, and growth factors occur at different levels in the alpha granules that contain them, due to factors such as stress levels and immune function," she said.

Beyond the hype

How well PRP will perform in the clinic remains to be seen.

"It makes sense that it should work; the question is where and how," said Jonathan Chang, MD, clinical assistant professor of orthopedics at the University of Southern California. "Conventional wisdom is always correct until you rigorously test it, and that's where we are right now. We need to test this very carefully and get beyond the hype, so we can figure out what it can be used for, and what is the right time to do so."

Fortunately, because PRP is an endogenous compound, investigating it involves few hazards.

"This is not a potentially dangerous intervention like gene therapy," said Craig Bottoni, MD, chief of sports medicine in the Orthopedic Surgery Service at Tripler Army Medical Center in Honolulu. "There's not much risk for patients, except maybe to their pocketbooks." (PRP therapy is not typically covered by insurance.)

Clinical applications

Bottoni is inclined to use PRP mainly when treating patients who are running out of options.

"I used it recently in a case of refractory patellar tendinopathy, because I don't have much else to offer," he said. "But I can't tell him that this is going to be the bomb, he's definitely going to get better. I'd be remiss in saying something like that."

Kim Harmon sees potential uses for PRP in both acute injuries and chronic conditions, though different problems may call for different PRP preparations.

"I think PRP may give you a better outcome in acute muscle injuries," she said.

She explained that when muscle tissue is torn, satellite cells can then make new muscle or scar tissue, and that NSAIDs (nonsteroidal anti-inflammatory drugs), commonly given for such injuries, may promote scar tissue rather than new muscle.[9,10] PRP, she thinks, may better support the formation of new muscle instead—but again, it has to be the right PRP.

Treatment benefits extend to bone

In addition to soft tissue injuries such as muscle tears or tendinopathy, PRP therapy shows promise in treating bone.

For example, in a study presented this February at the annual meeting of the American Academy of Orthopaedic Surgeons, patients with distal tibial fractures had significantly faster healing times than controls when treated with a mix of PRP, demineralized bone matrix, and mesenchymal stem cells. Average time to union was 71 days in the intervention group and 130 days in the controls.[1]

"It's not voodoo," said Mark Hardy, DPM, director of residency training at the Cleveland Clinic / Kaiser Permanente Foundation, who was not affiliated with the study. "With high-risk or revisional fusions, or with osteotomies, I'll either use PRP by itself or combine it with an off-the-shelf bone chip product. It's a lot cheaper than some of the other orthobiologics such as mesenchymal stem cells and bone morphogenic proteins."

Hardy reports radiographic confirmation of fusion at four to six weeks with the technique, versus three or four months without it. He emphasizes, however, that those results occur in his higher-risk patients—smokers, those with marginal vascular status, or patients taking immunosuppressive drugs for rheumatoid arthritis or connective tissue disease.

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"I separate the [PRP preparation] kits into two basic types," she continued. "The buffy-coat–based products—leukocyte-rich PRP—have higher platelet counts but they also contain white blood cells. There are questions, with acute injury, whether you want white cells in your PRP, because neutrophils can damage tissue. On the other hand, the plasma-based products—leukocyte-poor PRP—have a lower platelet count but they don't have many white cells. For an acute injury like a muscle tear, the most important growth factor is IGF-1, and there's very little of that in platelets; it's mostly in the plasma. So if you're treating an acute injury, a plasma-based product seems to me a better way to go."

Platelet activation is another difference between products that has clinical implications, Harmon said. When platelets are activated exogenously, they dump 90% of their growth factors within 10 minutes. But when they are activated by the patient's collagen after injection, the subsequent clotting forms a meshwork that traps the platelets, which continue to make growth factors for another three to seven days.

Sean Grambart prefers concentrations that don't require exogenous thrombin activation.

"You get an immediate burst versus a sustained release that way," he said. "Thrombin activation may also inhibit bone healing."

The choice about using PRP in acute conditions may come down to patience and economics, according to Harmon.

"From observation of our own and others' practices, we seem to be decreasing healing time by about a third," she said. "A three-week hamstring strain may become a two-week strain, or a six-week strain may become a four-week strain. For a professional football player, it may be worth the thousand dollars to do PRP; for me, I'm going to wait another week."

According to a retrospective study presented at the annual meeting of the American Academy of Orthopaedic Surgeons in February, however, use of PRP showed no advantage over routine rehabilitation methods in 10 pro football players with hamstring injuries, based on median time to return to play.[11]

In response, Harmon pointed out that like most PRP studies so far, this one was small and unblinded.

"I think PRP's main benefit in acute injuries may be improved outcome rather than quicker return to play," she said.

A commentary by Harmon, published last year in the *British Journal of Sports Medicine*, elucidates some of the issues and makes recommendations based on the existing evidence.[12]

Chronic conditions

"I think PRP therapy has the most potential for treating chronic conditions such as overuse tendinopathies," Bottoni said.

Many clinicians agree. The nature of tendinopathy offers clues as to why this might be so. It is not, as some assume, an inflammatory condition; rather, it occurs when chronic repetitive loading exceeds the tendon's adaptive capabilities, leading to microscopic tears and tissue degeneration.(6) The damage may accrue for months before symptoms such as pain and stiffness arise.

"When we look at tendons after they hurt for six weeks or so, there are no inflammatory cells there," Harmon said. "The tendons are degenerative; anti-inflammatory medication may relieve the pain, but it doesn't fix the problem. There are native tendon cells—tenocytes—that are not doing anything, because tendons are relatively biologically inactive. So the newer treatments for tendinosis, including PRP, try to stimulate healing."

In vitro, PRP compounds stimulate gene expression of the matrix molecules, collagen production, and tendon cell proliferation associated with healing.[13,14]

Harmon emphasizes, however, that other approaches such as eccentric exercises and tenotomy, as noted earlier, are her preferred first-line therapies. But when patients still don't get better, she turns to PRP. (It's worth noting that patients who had previously tried heavy load eccentric exercise were excluded from the aforementioned *JAMA* study.)

"In my patients, these are people who've been in pain an average of three years, who've tried everything," she said. "PRP is a last resort before surgery."

Patient selection is key, said Robert Monaco, MD, director of sports medicine at Rutgers and clinical assistant professor of medicine at the Robert Wood Johnson Hospital in New Brunswick, NJ.

"You really need to look at the pathology and make sure you're selecting the case appropriately," Monaco said. "We tend to reserve this for people who are really struggling, or for higher-end athletes for whom small differences and improvements can make significant changes in competition. I think it's an effective tool once you've exhausted everything else."

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