

Platelet-rich plasma injection

Could your patients benefit from a stab in the back?

by Gordon D. Ko, MD



Platelet-rich plasma (PRP) therapy has been in the news recently with publicized cases of professional football and baseball players undergoing the treatment. Notable athletes such as Tiger Woods and figure skater Patrick Chan have had PRP. Woodbine racehorses get it too. The use of PRP use has an extensive history, going back to 1987 in cardiac surgery.¹ PRP has since been used by specialists in ENT-maxillofacial-periodontal surgery, cosmetics, and burn wound healing.² In the past 10 years, PRP has also found uses in musculoskeletal medicine.³

What's involved?

PRP involves the injection of autologous blood concentrated with platelets back into the donor's body to promote healing. In PRP treatment, venous blood (up to 20-60 cc at one time) is taken out and then spun down over 14 minutes in a specially designed centrifuge. The platelet-concentrated portion (5x greater than normal serum) is withdrawn into a syringe and then injected into tissues to promote healing.⁴ Local anesthetic should be administered separately to the skin and subcutaneous tissues to minimize pain from the PRP procedure. It's generally not mixed with the PRP solution as dilution of the platelets may reduce effectiveness. Multiple injections are usually given over the injured area and repeated as needed over a period of time (typically once every 4 to 8 weeks) depending on the severity of injury and the healing response.

Procedure steps:

- 60 cc of venous blood is taken from the patient
- Placed in special Harvest centrifuge and spun for 14 minutes
- Platelet-rich plasma (includes buffy coat) is extracted out and mixed with citrate anticoagulant
- PRP is then injected into the sacroiliac ligaments to stabilize joint for long-term healing and mechanical pain reduction.

How it works

Platelets contain many different structures, including glycogen, lysosomes, alpha and beta granules. The main focus of PRP is the alpha granules, which house the growth factors essential for healing. These include: transforming growth factor beta (TGF β), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and epithelial growth factor (EGF). When the injected platelets are activated, these growth factors are released, triggering and amplifying the healing cascade.

TGF β acts during inflammation to help regulate cell migration and replication. VEGF is released after the inflammatory phase and stimulates angiogenesis, as well as synthesis of tendon cells and type 1 collagen. PDGF is responsible for promoting mesenchymal stem cell, osteoid and endothelial reproduction, along with collagen synthesis. EGF functions to produce basal skin cells and mucosal membranes, as well as inducing cell migration and replication.⁵ Other notable proteins found

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in PRP are vitronectin, fibronectin and fibrin, all of which function as cell adhesion molecules. Platelets also contain dense granules that contain factors (ADP, calcium, serotonin) that promote platelet aggregation. The activated growth factors are transported to the cell membrane for cellular export and paracrine signalling. These growth factors then bind to the surface receptors on the plasma membranes of their target cells. Some examples of these target cells include: mesenchymal stem cells, osteoblasts, fibroblast, endothelial cells and epidermal cells. The growth factor-receptor complex then signals for internal cellular proteins to activate specific gene sequences that allow for functions such as: cellular reproduction, matrix formation, osteoid production and collagen synthesis.

How safe is PRP?

Since PRP uses autologous blood, any chances of immunogenic reactions are negated, as well as disease transfer that may occur from the usage of non-autologous blood. Acting growth factors attach to cell surfaces rather than the nucleus, minimizing the chance of tumour formation through the use of negative feedback control. One concern that had arisen was the former use of bovine thrombin as the clot initiation factor in the PRP treatment in surgical grafting and intra-articular injections. Complications included bleeding coagulopathies from antibodies to such clotting factors. Since 1997, production has eliminated contamination of factor Va in such thrombin with no further reports of such complications. With the remote risk of prion disease, it's still best to avoid bovine thrombin altogether. Instead, autologous fat cells can be used for activation purposes.

As with all injection procedures, of course, there are remote chances of local anesthetic allergy and toxicity, needle trauma, breakage or infection.

Contraindications to PRP include

- low platelet count (< 105/uL)
- low hemoglobin (< 10 g/dL)
- low blood pressure — hemodynamic instability
- dysfunctional platelets and clotting (hemophiliac)
- consistent use of NSAIDs (anti-inflammatory drugs) within 48 hours of PRP procedure
- corticosteroid injection at treatment site within 2 weeks of PRP procedure
- corticosteroid by mouth or IV within 2 weeks of PRP
- concurrent or recent fever or illness. Septicemia (generalized blood infection)
- active history of Psuedomonas, Enterococcus or Klebsiella infections (PRP in one study was shown to potentially stimulate these pathogens)
- cancer — especially hematopoetic or of bone
- rash at injection site

Is it effective?

For bone fracture healing, there is equivocal consensus. Some studies support such an effect and others do not. Longer randomized clinical trials (RCTs) are currently ongoing. The state of the evidence for PRP in musculoskeletal pain is summarized below.

Tennis elbow

A randomized controlled trial compared PRP (51 patients) to corticosteroid injections (49 patients). The primary outcome measure was a 25% reduction in VAS pain or DASH (Disabilities of the Arm, Shoulder, Hand) score without need for a reintervention after 1 year. Seventy-three percent of the PRP vs 49% of the corticosteroid patients were success-

ful ($p < 0.001$). The corticosteroid group was better initially and then declined, whereas the PRP group progressively improved.⁷

Achilles tendon

A study by Sanchez et al followed 12 athletes who underwent open suture repair of the Achilles tendon after complete tearing of the tendon. Half of the patients received surgery in a growth factor rich preparation (GFRP), while the remaining 6 patients underwent conventional surgery. The results of the surgeries were based on: range of motion, functional recovery and complications. The 6 athletes with exposure to the GFRP were able to recover their range of motion in 5-9 weeks, while it took 8-14 weeks for the patients of the control group to do the same. The experiment group patients were also able to take up gentle running sooner, and the cross sectional area of the recovered tendon was less than that of the control group.⁸ An earlier rat Achilles tendon transection study demonstrated that mechanical stimulation was a prerequisite for platelets to work by day 14. In rats, both activity cages and platelets increased repair

independently of each other.⁹ This also may provide some rationale for the lack of a significant benefit in a recently published RCT of Achilles tendinopathy. Fifty-four subjects were injected with either PRP or saline over 24 weeks. Both groups received eccentric exercises (straightening joints against resistance) and both significantly improved.¹⁰ This confounding variable of exercise was also similarly seen in a two-year RCT with dextrose prolotherapy for low back pain.¹¹

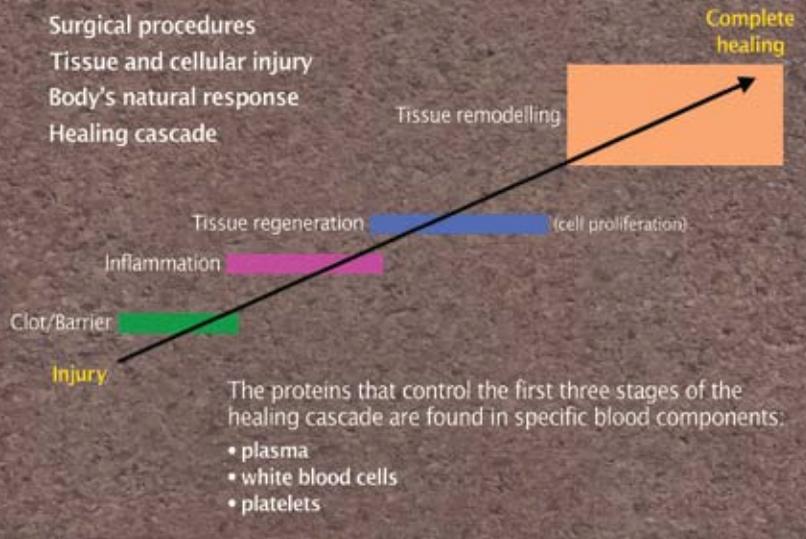
Plantar fasciitis

Barrett et al performed a study in which 9 patients with thickened plantar fascia were treated with 3 cc of autologous platelet concentrate (APC+) injections. The patients were then subjected to a lower leg brace for 2 days and monitored regularly for a year. Results of the study — obtained through ultrasound readings — indicated that the bands of the plantar fascia significantly decreased in thickness, thus signifying reduced swelling. Of the 9 patients who partook in the study, 6 had fully recovered from all symptoms at 2 months. One patient recovered after dropping out of the experiment (due to corticosteroid usage), one showed improvement after a few more injections of APC+, and the last patient still felt pain during walking.¹²

Anterior cruciate ligament (ACL) repairs

Ventura et al performed a study to test the efficacy of growth factors on ACL surgery recovery. Twenty patients with laxity due to torn ACL underwent surgery using autologous hamstring tendons. The patients were divided into one of two groups: growth factor treated and control. The experimental group was treated with growth factors similar to the ones obtained from PRP. Results after 6 months indicated that the patients in the experiment group had denser ACLs after recovery, with a density similar to the posterior ligament. One patient had a synovitic reaction, with

Natural healing cascade



Factors that may impair collagen synthesis and tendon-ligament healing

- prior to PRP, it's important to screen for and correct conditions that could impair healing. These include:
 - nutritional deficiencies: iron studies, serum zinc, serum vitamin C. With neuropathic pain, screen also for 25 (OH) vitamin D₃, serum B₁₂, RBC folate, omega 3 fatty acid profile
 - hormonal deficiencies: TSH (hypothyroidism), DHEA-S/Cortisol A.M. (adrenal fatigue), free testosterone (hypogonadism), IGF-1 (adult growth hormone deficiency syndrome), FBS and A_{1c} (diabetes)
 - inflammatory disorders: ESR, CRP, CK, seronegative disease and immunological workup (as indicated based on the clinical examination)

hypertrophic tissue.¹³ A canine ACL study showed that ACL defects treated with platelets had a 40% increase in strength at 6 weeks vs 14% for those untreated with platelets.¹⁴ Other arthroscopic enhanced repairs include articular cartilage avulsion¹⁵ and foot-ankle surgeries.¹⁶ But the role of growth factors in enhancing bone repair remains controversial, as they possibly inhibit osteogenic action of bone morphogenetic proteins.¹⁷

Rotator cuff repairs

PRP-enhanced rotator cuff arthroscopic repairs have been described in the past.¹⁸ But for more definitive data, we await the completion of a National Institutes for Health (NIH) sponsored study underway at Sunnybrook Health Sciences Centre.

The bottom line

There's emerging evidence for PRP in the treatment of chronic ligament and tendon injuries. Some studies appear to be confounded by

incorporating exercise as a variable. The strongest evidence to date involves randomized controlled trials (RCTs) for tennis elbow. There are supportive smaller trials for other musculoskeletal tendon/ligament pain conditions. Case reports suggest possible benefit in muscle tears. There's conflicting evidence on the use of PRP in bone healing. There may also be applicability to the commonest cause of disability in industrialized nations: chronic low back pain. We've successfully treated a number of cases of sacroiliac joint instability with PRP prolotherapy in our clinic. But further RCTs are required to support more funding for this and for other interventions, and to delineate the patient and disease variables that will respond best to this emerging treatment. **PE**

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