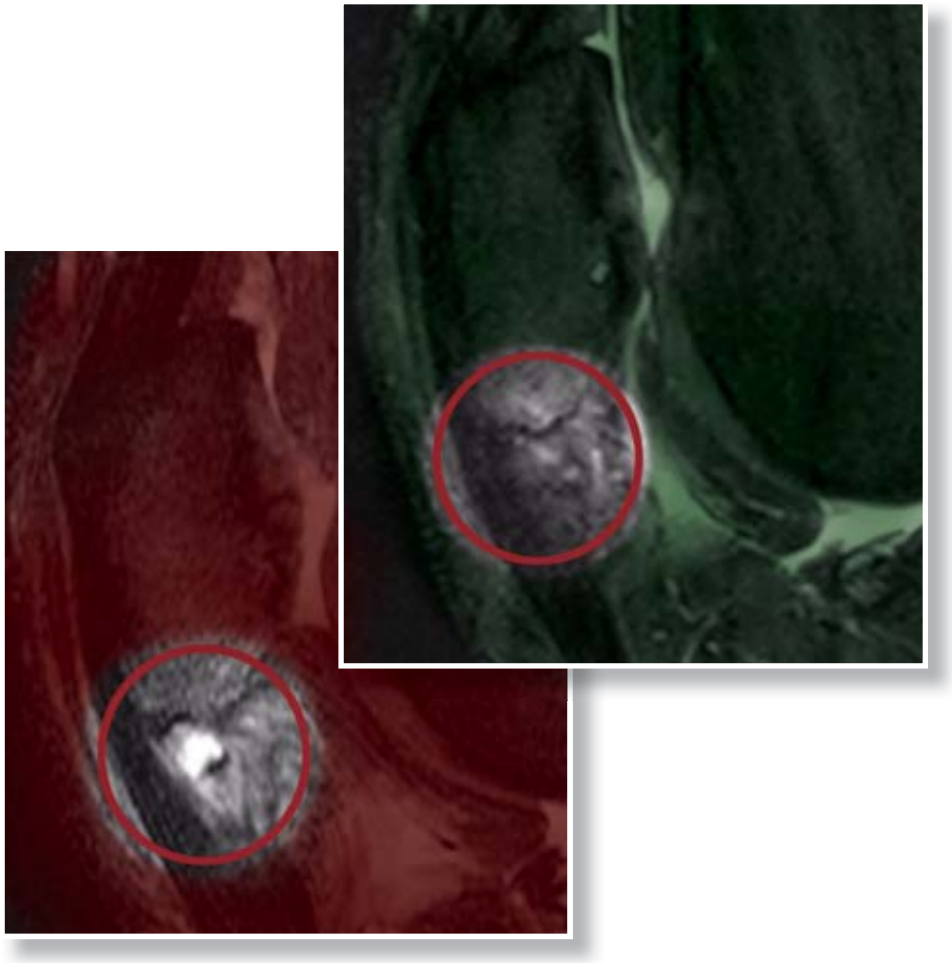
# Regenerative Medicine In Pain Management



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Regenerative medicine, where the body regenerates or rebuilds itself, is a relatively new and rapidly evolving front in the field of interventional pain management. Although stem cell therapy has garnered much of the attention over the past several decades, multiple other regenerative medicine modalities also have caught the public's attention. As experts in our field, we should be ascertaining if and when to offer these treatments to our patients.

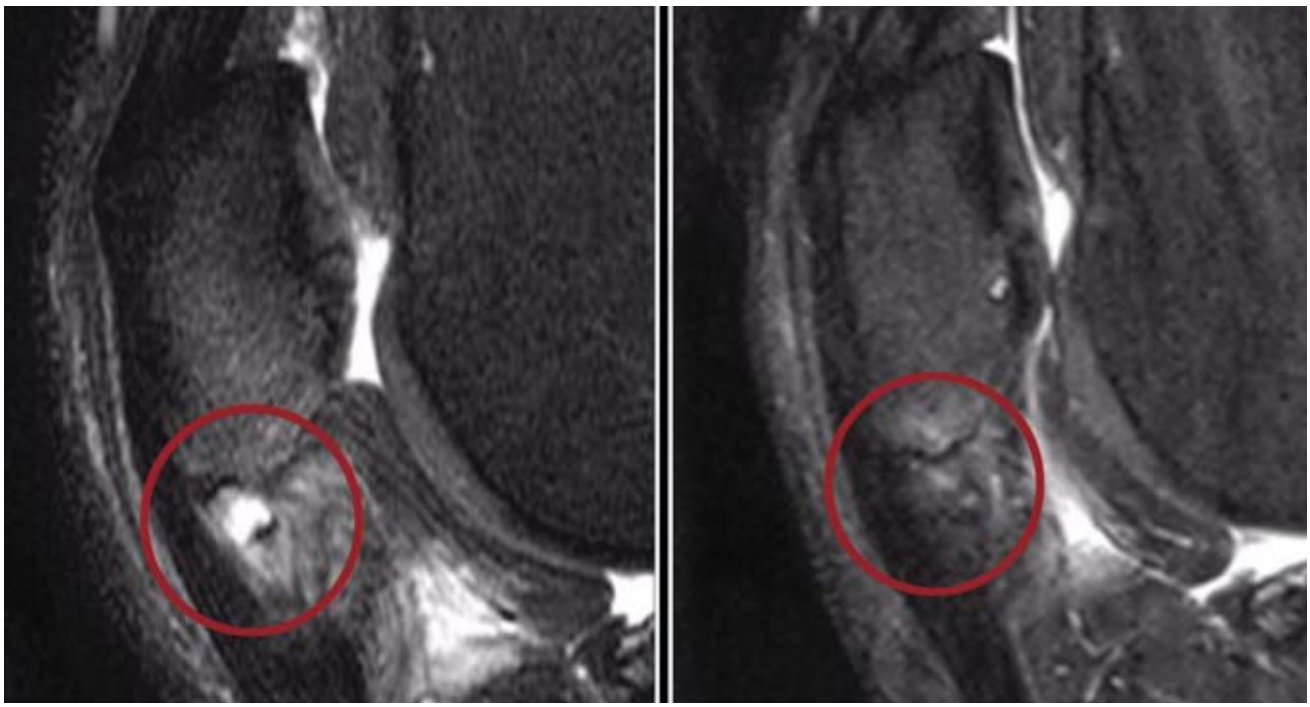

**Figure. A 42-year-old man with patella tendon tear (left). Over the course of 1 year, the man received 3 ultrasound-guided platelet-rich plasma injections with magnetic resonance imaging showing near complete resolution (right).**

Images courtesy of Rahul Desai, MD, of Epic Imaging in Portland, Oregon.

## Stem Cells

Stem cells are characterized by the ability to renew themselves through cell division and differentiate into a diverse range of specialized cell types. There are multiple sources of stem cells, including human embryos, which contain pluripotent stem cells that can differentiate into any cell line. Human embryonic stem cell use has been and currently remains an ethically controversial topic. Induced pluripotent stem cells are generated by taking cells, such as skin cells, from a person and then injecting a small number of specific genes or molecules into the cells, which converts the cells into stem cells. A concern with this source of stem cells is introducing an oncogene, which can result in cancer. Adult stem cells are another category. Example sources of adult stem cells include bone marrow, peripheral blood, placental blood, placental tissue, and adipose tissue. Most adult stem cells are multipotent, which can differentiate into some, but not all cell types.

Stem cell technology has been used clinically since the 1960s, in the form of bone marrow transplants to treat conditions like leukemia. Since then, much research has focused on stem cell therapy and its application to a variety of medical conditions. For interventional pain applications, ongoing research is examining the application of stem cell therapy for the treatment of multiple chronic pain conditions, such as osteoarthritis and degenerative disk disease. Crevensten et al studied the effects of injecting mesenchymal stem cells into degenerative disks in rats and found a trend of increased disk height, suggesting an increase in matrix synthesis in the study group compared with the control subjects.[1] Mesoblast is conducting the second phase of research on mesenchymal stem cell from bone marrow for degenerative disk disease in human subjects. Many interventional pain physicians are hopeful that stem cells will prove to be an effective treatment for conditions such as diskogenic pain, which currently has few treatment choices.

Future research should assess the relative effectiveness of the different stem cell sources to treat different types of pain conditions. This will help guide the choice of the source of stem cells to use and the types of conditions to treat.

## Amniotic Membrane

Because of its unique properties and availability, the human amniotic membrane recently has been studied and is currently being used in regenerative medicine. The human amniotic membrane is composed of 2 cell types, human amnion epithelial cells and human amnion mesenchymal stromal cells. Both types display low immunogenicity and display characteristic properties of stem cells. Both cell types are able to differentiate in vitro into the major mesodermal lineages.[2]

Human amniotic membranes have been used extensively in ophthalmology and plastic surgery for the treatment of corneal and cutaneous wounds, respectively.[3] Recent research has focused on the use of human amniotic membranes applied to other disciplines. Intraoperative placement of amniotic tissue at the site of laminectomy in dogs was effective in reducing epidural fibrosis and scar adhesion.[4] Using a human amnion tissue patch after a right L4-5 decompression procedure significantly reduced both scar tissue formation and adherence to the underlying dura in the patient.[5]

The application of human amniotic membranes within the field of interventional pain management is currently a topic of great interest. Much of the current research is investigating its role in the treatment of tissue damage and inflammation, such as tendonosis and tendonitis. After an intralesional injection of ovine amniotic epithelial cells into equine superficial digital flexor tendon defects, the amniotic epithelial cells participated in the deposition of new collagen fibers in the repairing area.[6] Amniotic epithelial cells injected into calcaneal tendon defects in sheep resulted in a high number of reparative cells in active proliferation that were accumulating collagen within the extracellular matrix.[7] Injecting amniotic epithelial cells into Achilles tendon defects in sheep resulted in much better structural and mechanical recoveries than control tendon defects during the early phase of healing.[8]

Additional research in the field of human amniotic membrane applications in interventional pain management is needed, but animal model research studies and anecdotal reports of its use in human subjects are promising.

## Platelet-Rich Plasma

Platelet-rich plasma (PRP) therapy was first introduced in the 1970s and has been used in many medical specialties, including orthopedic surgery, plastic surgery, sports medicine, wound care, and pain management, since the 1990s. PRP therapy involves the injection of concentrated platelets, autologous growth factors, and secretory proteins into the region of interest. PRP has been used for numerous conditions. In interventional pain management, it is commonly used for acute and chronic conditions such as tendinopathy, tendonosis, muscle strain, muscle fibrosis, ligamentous injury, arthritis, arthrofibrosis, articular cartilage defects, meniscal injury, and chronic synovitis or joint inflammation (Figure).[9]

The PRP concentrate is made from the patient's own blood. After the blood is centrifuged, it separates into the serum (top coat), the platelets and white blood cells (buffy coat or middle layer), and the red blood cells (bottom layer). The middle layer contains a platelet concentration of at least 1 million platelets/uL (normal range: 150,000—350,000 platelets/uL) and a 3- to 5-fold increase in growth factor concentrations.[10] There is significant variability between PRP centrifuge systems, each yielding varying products. There is no clear comparative evidence to date indicating a superior product. Some PRP protocols include white blood cells, whereas others involve activation with thrombin or calcium, and the platelet concentrations vary as well. The optimal concentration of platelets for PRP is debated. Giusti et al examined the optimal concentration of platelets for promoting angiogenesis in human endothelial cells and found 1.5 million platelets/uL to be the optimal concentration.[11] With the system used in our practice, 20 cc of blood will yield approximately 3 cc of concentrate, adequate for small target areas like an epicondyle or acromioclavicular joint and 60 cc of blood will yield 7 to 10 cc of PRP for larger applications, such as a hip or shoulder injection.

Platelets synthesize and release more than 1,100 biologically active proteins, including those that promote tissue regeneration.[12] PRP is thought to enhance the recruitment, proliferation, and differentiation of cells involved in tissue regeneration to promote healing.[10] Studies have demonstrated that PRP positively affects gene expression and matrix synthesis in tendons. Cell proliferation and total collagen production is increased in human tenocytes cultured in PRP. In vivo, a platelet concentrate injected into the hematoma 6 hours after creation of a defect in a rat Achilles tendon demonstrated increased tendon callus strength and stiffness. Muscles treated with insulin-like growth factor-1 and basic fibroblast growth factor showed improved healing and significantly increased fast-twitch and tetanus strength.

Over the past decade, numerous published studies involving human subjects have emerged investigating the use of PRP for conditions such as lateral epicondylitis, patellar tendinopathy, Achilles tendinopathy, rotator cuff tendinopathy, rotator cuff tears, medial collateral ligament and anterior cruciate ligament tears, and osteoarthritis of the knee.[13] Although most of the studies examined small populations, the

results have been very promising, with many demonstrating significant pain relief and functional improvement. Future studies are needed in this emerging field to further delineate the optimal constituents and concentrations of the PRP solution and more clearly define the role of PRP in interventional pain management.

## Conclusions

Osteoarthritis and other degenerative conditions, which are largely a function of aging, are a major area of concern for pain physicians. Regenerative medicine is an exciting and rapidly evolving branch of medicine, which has the potential to let us turn back the clock and regenerate worn-out tissues. Based on current data, it is reasonable to integrate these regenerative techniques into treatment algorithms, usually after other traditional treatments have failed. As research progresses, if more conclusive evidence demonstrates superior efficacy over other modalities, the use of regenerative medicine techniques would be justified sooner in the treatment algorithm.

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