What is Prolotherapy?

Simply stated, prolotherapy is a technique to strengthen and rejuvenate injured or weak ligaments and tendons and resolve joint laxity. As a consequence, a patient’s problems with pain and loss of function are markedly diminished or resolved. This is done by identifying the areas of weakness and stimulating the incomplete healing process with injections of natural occurring therapeutic agents that provoke the acute inflammatory response and healing cascade including the influx of stem cells to promote renewal of damaged tissues. The temporary, low grade inflammatory response at the site of injection draws in fibroblasts to synthesize collagen and strengthen cartilage. It also provokes the production of growth factors that restart the healing cascade that never completed effective healing. (1-7)

The process of prolotherapy is pretty straightforward: the affected areas are examined, identified and anatomy is marked using landmarks and ultrasound to visualize structures. The skin is anesthetized with lidocaine or procaine, the area cleaned with Hibiclens. The identified structures are then injected with the therapeutic agent using anatomic landmarks or ultrasound guidance. This process provokes the acute reaction during which time patients are to avoid NSAIDs. A series of treatments every 3 to 4 weeks provokes the steady improvement of structure strength and reduction of pain. The number of treatments can be as few as one or as many as 20. The usual range is 3 to 6 times.

The roots of prolotherapy extend all the way back to ancient Egypt. The master physician Imhotep wrote about using fiery brands to scar the tendons of horses whose shoulders were dislocated in battle. Modern techniques are markedly more sophisticated and gentle compared to those days. The modern era of prolotherapy was ushered in by Earl Gedney DO who developed a technique to repair his own injured thumb. He injected an irritating substance into his ligaments when his colleagues had no options to help him.(8) The first article on prolotherapy was published by Dr. Gedney in 1937 describing his technique and two successful case studies treating a chronic knee and chronic back pain patient(9). Prolotherapy was further evolved by Dr. George Hackett and Dr. Gus Hemwall to the primary aspects as to how it is practiced today. However, many significant advances in medical knowledge in the last twenty years have ushered in an entirely new level of effectiveness and safety to prolotherapy. These changes include introduction of Platelet Rich Plasma (PRP) and Autologous Stem Cell Therapy (ASCT), described later in this article.
Prolotherapy is practiced by physicians in the United States and worldwide, shown to be effective for tendinopathies, ligament sprains, back and neck pain, joint laxity and instability, plantar fasciitis, rotator cuff syndrome, and arthritis. The Mayo Clinic has endorsed prolotherapy as an option if conservative treatment strategies have failed. (10)

**What is Platelet Rich Plasma (PRP) Therapy?**

PRP is produced by drawing a patient’s blood and using a special centrifuge that concentrates the platelets 4 to 5 fold. Platelets contain a number of proteins and other bioactive agents that initiate and regulate the wound healing cascade. These include multiple growth factors that stimulate cell replication, angiogenesis, and proliferation of myoblasts and mediate repair of skeletal muscle (11-13). This process is markedly accelerated with the concentration of platelets in PRP (14). Importantly, activated platelets “call” in adult stem cells to the injury site and accelerate the healing process. PRP has been used since the early 1990s to promote injury repair in multiple clinical settings (15-18). Initially, preparing PRP required large and extremely expensive machines found only in hospitals. The evolution of technology has now placed the centrifuges in the office setting, making PRP safe, simple and inexpensive to produce for a patient treatment. Concerns about growth factors causing cancer have never proven out- there has never been a case of neoplasia related to PRP administration (19). This is because PRP works through the normal healing cascade, never entering cells but rather interacting with surface receptors of mesenchymal stem cells, fibroblasts, endothelial cells and epidermal cells (20). There is no direct interaction with cellular DNA. Thus, there is no possibility of inducing tumor formation (20). Since the blood is drawn from the patient there is little to no risk of immune reaction or infection (21) and even appears to have antibacterial properties (22).

**Why Not Steroid Injections?**

Steroid injections are used extensively to treat a wide range of injuries and chronic problems that overlap with the realm of prolotherapy’s treatment success. Why not use steroids? As the “ultimate anti-inflammatory” steroids produce short term inhibition of inflammatory process. This results in reduction in pain. However, steroids also do nothing about the underlying problem with the ligament or tendon and actually slowly weaken them with repeated injections. Further, steroids have a large number of potentially severe adverse reactions and risks such that their use is significantly restricted to a few injections in a 12 month period (23-26). A head-to-head study comparing steroid injections to prolotherapy demonstrated that prolotherapy exceeded steroid injections for reduction of pain and improvement of function (27). And, of course, it addresses the real underlying problem behind the ligament or tendon weakness.
**Stem Cell Prolotherapy: The Future is Now**

Drawing upon further advances in scientific knowledge we are now able to harvest, concentrate and utilize adult stem cells from the patient (autologous). In contrast to fetal stem cells which have the ability to transform into any cell type, adult stem cells are partially differentiated. These cells are found throughout the body but in large concentrations in the bone and especially in adipose tissue. One type of these partially differentiated adult stem cells is known as mesenchymal stem cells (MSCs) which differentiate to musculoskeletal structures including ligaments, tendons as well as cartilage and produce bioactive cytokines that promote healing, repair and replacement of injured tissues. Their use has been deemed safe for use in humans since 1995(29) and their ability to identify specific areas of tissue injury are well studied (30-32). In osteoarthritis, an issue for 27 million Americans (33), stem cell potency is depleted with reduced capacity to proliferate and differentiate (35, 36). Techniques have now been developed to isolate the MSCs and encourage them to differentiate into the needed tissues.(37) Extensive research has documented the effectiveness of stem cell therapy to trigger regeneration of articular cartilage, meniscal tissues, with reduction of osteophytic remodeling and subchondral remodeling seen in osteoarthritis (34, 38-41).

Stem cells can be derived from both bone marrow (bone marrow aspirate concentrate- BMAC) and adipose tissue (adipose derived stem cells – ADSC) and then concentrated to increase their efficacy (42, 43). There is growing evidence that the combination of bone marrow stem cells with PRP is equivalent to autologous bone grafting (44). BMAC has been used extensively for multiple nonunion of fractures including tibia, metatarsals, hip osteonecrosis (45-49). Adipose tissue is a rich source of stem cells with extensive proliferative and differentiation capacity. (50-52). The MSCs from adipose tissue are easily isolated and used with PRP to promote repair and regeneration of musculoskeletal tissues. The PRP fat graft appears to be induced by its environment to produce the cell types that surround it. (53). ADSC harvesting is simpler in the office and more comfortable for patients than BMAC. Also, the yield of stem cells is much higher in ADSC vs. BMAC by a ratio of 500 to 1000:1 indicating markedly greater potential efficacy of the treatment (54).

Autologous stem cells fall under the regulation of the FDA but any regulation is eliminated if the physician follows the FDA’s rules including harvesting and implanting the stem cells in the same surgical procedure (55,56)

**Musculoskeletal Ultrasound**

Dramatic improvement in image quality and reductions in price for small, mobile ultrasound units has lead to high quality, real time imaging of ligaments, tendons, cartilage and their forms of pathology. Although imaging technology is no substitute for clinical common sense,
ultrasound can expand information for making good therapeutic decisions and improve accuracy and safety of treatment.

Who is the Appropriate Patient for Referral?

As clinicians, we are always finding ways to improve our clinical care for patients. Inevitably we find patients who are slow or unresponsive to therapeutic interventions. You may have a patient with unresolved or recurrent musculoskeletal pain problems. He/she want to avoid steroid injections, chronic pain medications or surgery and pursue approaches that support the normal healing process. If so, you may have a patient who would benefit from prolotherapy. Please feel free to contact me to review the person’s concerns and whether prolotherapy is an appropriate alternative.

References

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