The Role of Regenerative Medicine in the Treatment of Sports Injuries

Gerard Malanga, MD[a,b,*], Reina Nakamura, MD[a]

KEYWORDS

• Regenerative medicine • Stem cell therapy • Platelet-rich plasma • Biological agents • Sports injuries • Tendon • Ligament • Cartilage

KEY POINTS

- Regenerative medicine is of particular interest in the treatment of sports injuries, as historical and recent evidence increasingly refute the commonly used treatments of anti-inflammatory medications and corticosteroid injections.
- The use of biological treatments using a patient's own stem cells and growth factors to heal damaged tissues is an attractive option.
- Use of these treatments in conjunction with aggressive/comprehensive rehabilitation may maximize nonsurgical treatments of these various sports injuries.
- More rigorous studies using these biological agents to treat such injuries could potentially change the way most sports injuries are managed.
- The true utility of regenerative medicine for sports injuries will become clearer as more high-quality research is published.

INTRODUCTION

The treatment of sports injuries historically has included the use of the PRICE principle (Protection, Rest, Ice/cold, Compression, and Elevation), analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs), and, commonly, corticosteroids. The PRICE principle, widely used in the initial treatment of soft-tissue sports injury, is thought to generally reduce hemorrhage into the injured area and thereby reduce pain and swelling.[1] Rest is recommended to minimize additional stress or strain to promote healing, while cooling decreases bleeding and ultimately serves as a counterirritant to reduce pain.[2] Both compression and elevation work to control swelling.[2] The clinical basis for the

[a] Department of Physical Medicine & Rehabilitation, Rutgers University-New Jersey Medical School, Newark, NJ 07103, USA; [b] New Jersey Regenerative Institute, 197 Ridgedale Avenue, Cedar Knolls, NJ 07927, USA
* Corresponding author. New Jersey Regenerative Institute, 197 Ridgedale Avenue, Cedar Knolls, NJ 07927.
E-mail address: gmalangamd@hotmail.com

Phys Med Rehabil Clin N Am 25 (2014) 881–895
http://dx.doi.org/10.1016/j.pmr.2014.06.007 **pmr.theclinics.com**
1047-9651/14/$ – see front matter

application of the PRICE principle is well supported in experimental studies, though not by randomized controlled clinical trials.[1]

NSAIDs are often used during and after acute injuries, and in chronic overuse injuries to control pain and inflammation.[3] As a class of medications, they have varying effects on inflammation, analgesia, and fever. NSAIDs work to inhibit the cyclooxygenase enzymes from which prostaglandins, prostacyclins, and thromboxanes are produced from arachidonic acid.[4] Cyclooxygenase has 2 isoforms, COX-1 and COX-2.[4] Whereas COX-1 is physiologic and is present in numerous tissues in the body, COX-2 is released in response to injury.[4] This isoform produces compounds that increase temperature, sensitize pain receptors, and play a role in inflammation.[4] NSAIDs are used in sports injuries for their capabilities to inhibit COX-2, and are available as general cyclooxygenase inhibitors or COX-2–specific inhibitors.[4]

NSAIDs have significant side effects, most notably in the upper gastrointestinal tract,[5] which include gastrointestinal perforation/hemorrhage, peptic ulcer disease, abdominal pain, diarrhea, nausea/vomiting, and stricture formation.[5] Other effects such as hypertension, congestive heart failure, renal insufficiency, and hyperkalemia have been reported.[5] Furthermore, ibuprofen may potentially inhibit aspirin's antiplatelet activity.[5] A review of NSAIDs on various acute sports soft-tissue injuries showed that NSAIDs have a modest role in the treatment of acute injuries, without harmful effects when used for a short period.[3] Ibuprofen, celecoxib, and diclofenac decreased synovial fluid levels of tumor necrosis factor α, interleukin-6, and vascular endothelial growth factor (VEGF), which in turn significantly improved patient Western Ontario and McMaster scores in a dose-dependent fashion after 14 days of treatment.[6]

Injectable corticosteroids are another class of medications frequently used to treat sports injuries because of their anti-inflammatory effects. Corticosteroids inhibit cyclooxygenase enzyme isoforms and lipoxygenase, which converts arachidonic acid to leukotrienes.[7] These compounds play a key role in chemotaxis and inflammation, which is the rationale for their ubiquitous use in sports injuries. Side effects include corticosteroid-induced cutaneous atrophy, hyperglucocorticoidism, temporary deterioration of diabetes mellitus, facial flushing, and anaphylaxis.[5]

Historical and recent evidence increasingly refute the commonly used treatments of anti-inflammatory medications and corticosteroid injections for most sports injuries. This view holds particularly true for tendinopathies. Cohen and colleagues[8] revealed that indomethacin and celecoxib had a negative effect on rotator cuff tendon-to-bone healing, and organization of collagen fibrils in a murine model. Coombes and colleagues[9] conducted a meta-analysis on the effect of corticosteroids in various tendons in comparison with other nonsurgical interventions. Although corticosteroids provided short-term (0–12 weeks) benefit, there was a decline in function and increased pain from intermediate (13–26 weeks) to long term (>1 year) for lateral epicondylalgia.[10] Short-term effectiveness for rotator cuff tendon was inconclusive, and no significant difference was noted regarding intermediate and long-term results.[10] There was a short-term decrease in pain for patellar tendon, but not for Achilles tendon.[10] In a randomized placebo-controlled trial of unilateral epicondylalgia, the same group reported that patients treated with corticosteroid injection had poorer outcome and higher recurrence after 1 year.[10] The corticosteroid group had better outcomes than the placebo group at 4 weeks, although this difference was not significant when physical therapy was taken into account. At 26 weeks and 1 year, patients who received corticosteroid had poorer outcomes in comparison with placebo.

Tendinopathy, also referred to as tendinosis, is a very common injury presenting to sports medicine physicians. These injuries have previously been improperly named tendonitis, implying the presence of an inflammatory process.[11] It is now well