The Role of Regenerative Medicine in the Treatment of Sports Injuries

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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

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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

recognized that chronic tendon complaints are an overuse injury that is degenerative in nature.[8] Contributing factors to tendinopathy pain include excessive load or frequent microtrauma, in addition to intrinsic biomechanical changes predisposing to injury.[8]

The pain accompanying tendinosis was previously thought to be due to inflammation; however, it is now known that tendinosis is histologically characterized by random and disorganized structure, hypercellularity, and neovascularization, and is devoid of inflammatory cells.[8] Although the exact mediators of pain are uncertain, irritants and neurotransmitters seem to play a role; these include lactic acid, glutamate, and substance P.[8]

Healing and repair of a tendon occurs in 3 stages.[8] The inflammatory phase in the first few days is characterized by inflammation and migration of erythrocytes and polymorphonuclear leukocytes.[8] Monocytes and macrophages are also present for phagocytosis of necrotic tissue.[8] Chemokines are released, leading to chemotaxis of tenocytes, which lay down collagen III.[8] This process is followed by the proliferative phase, which is characterized by more collagen III and increased ground substance, lasting several weeks.[8] From week 6 up to 1 year, remodeling takes place.[8] Collagen I is synthesized along the path of stress,[8] followed by scar formation.[8] Ligament and muscle injuries undergo basic stages of healing similar to those of tendons.

Based on the current literature, it is the opinion of the author that NSAIDs play a minor role, if any, in most postacute sports injuries, and may even truncate the healing response by interfering with physiology. A short course, (ie, 7–10 days) may be of benefit during the initial acute inflammatory phase of treatment. Similarly, although corticosteroids may offer short-term relief of symptoms, it is likely more harmful in the long term, for the same reasons.

The key to the successful treatment of most sports injuries, following the control of the initial pain and inflammation phase, is a functional rehabilitation program stressing restoration of normal range of motion, strength, and proprioceptive training, with a gradual return-to-sport program.

REGENERATIVE BIOLOGICAL TREATMENTS

The application of regenerative biological treatments for ailments of the musculoskeletal system emerged in the 1930s.[12] The purpose of regenerative medicine is to heal a pathologic process by augmenting the body's physiology by nature or by means of bioengineering.[12] The current practice of regenerative medicine encompasses prolotherapy, platelet-rich plasma (PRP), and mesenchymal stem cell therapy (**Table 1**).[12]

Table 1
Various regenerative treatments and their mechanism of action

Treatment	Mechanism of Action
Prolotherapy	Introduce irritating agent Trigger inflammatory cascade Proliferation of fibroblasts, deposition of collagen Healing
Platelet-rich plasma	Degranulation of activated platelets Increased vascular permeability leading to chemotaxis of inflammatory cells Cellular proliferation and formation of extrafibrillar matrix Formation of collagen
Stem cell therapy	Cells differentiate into various cells in the mesenchymal lineage including bone, cartilage, adipose, and other soft tissues

Prolotherapy

Prolotherapy introduces an irritating agent to pathologic tissue to obtain a healing response.[12] It first emerged in the musculoskeletal literature in the 1950s, although the concept has been around since the 1930s and possibly dates back to the time of Ancient Greek and Egyptian medicine.[12] Although the exact mechanism of prolotherapy is uncertain, it is postulated that proliferant solutions increase collagen synthesis and cause transient neurolysis,[12] which is accomplished by cytokines that mediate chemomodulation and chemoneuromodulation.[12] The irritating vehicles, which include hyperosmolar dextrose, zinc sulfate, glycerin, phenol, guaiacol, pumic acid, and sodium morrhuate, are theorized to trigger the inflammatory cascade that ultimately leads to proliferation of fibroblasts and deposition of collagen.[12] Although animal studies on tendons show benefit, the results on ligaments are inconclusive.[12]

In humans, prolotherapy has been shown to be an effective treatment for the symptoms of pain in various sports injuries including groin pain, Achilles tendinosis, and plantar fasciitis.[13–16] In a pilot study including 24 patients with chronic lateral epicondylar pain, Scarpone and colleagues[17] found that an injection of a 10.7% dextrose/14.7% sodium morrhuate solution given every 4 weeks at baseline, 4, and 8 weeks, offered significant improvement in pain and isometric contraction strength 16 weeks after treatment when compared with baseline and controls.

In a randomized study, Yelland and colleagues[14] compared prolotherapy with eccentric loading exercises for Achilles tendinosis. Although there was improved pain in favor of prolotherapy at 6 months, and prolotherapy combined with eccentric loading exercises at 12 months, the differences were not significant in the long term.[14] Despite encouraging results, there are few quality trials with rigorous medical evidence from which to build a general consensus regarding prolotherapy and its use in sports injuries.

Platelet-Rich Plasma

PRP is broadly defined as plasma with platelet concentration higher than baseline.[18,19] However, the concentration of platelets necessary to induce a healing response is thought to require a minimum of 1 million platelets per microliter in 5 mL of plasma.[19–21] This burden necessitates centrifugation of whole blood to separate the various components, which include red blood cells, platelet-poor plasma, and a layer of PRP. Platelets have been well known to participate in blood-clot formation and in modulation of inflammation and healing, achieved through release of various growth factors, cytokines, and chemokines contained in mitochondria, dense granules, α granules, and lysosomal granules.[22] Eicosanoids are also newly synthesized from arachidonic acid, partaking in the process of inflammation.[22] Degranulation of 70% to 95% of growth factors occurs within 10 minutes of activation, with the remainder slowly released over a few days.[19,21] Various methods of processing autologous venous blood exist with the goal of platelet concentration, activation, and release of bioactive proteins.[23]

PRP is typically made in a 2-step centrifugation process.[23] The first cycle separates venous blood into red blood cells, platelet-poor plasma, and a buffy coat.[23] The platelets and leukocytes separate into the buffy coat.[23] The second step isolates the buffy coat from the other 2 layers for application.[23] Because the layers are separated by pipette, this process is subject to human error and therefore is imprecise.

Multiple devices are now available to process PRP, each yielding various concentrations of platelets, white blood cells, and red blood cells. The clinical significance of differing concentrations of cells is uncertain. Mazzocca and colleagues[24] studied the effect of various PRP preparations and concentrations on cells of bone, muscle,

and tendon. The investigators were unable to conclude which preparation was best suited to treat the various cell types in vitro, and also noted that a higher concentration of platelets did not necessarily result in better outcomes.

Dense granules contain serotonin, histamine, dopamine, calcium, and adenosine.[20] Serotonin and histamine increase vascular permeability, allowing movement of cells that participate in inflammation to the area.[20] This process results in activation of macrophages and chemotaxis of polymorphonuclear cells.[20] Cellular proliferation and formation of extrafibrillar matrix follows, which leads to formation of collagen.[20] This process works in synergy with other growth factors and cytokines released from platelets.

The α granules in platelets are mostly composed of transforming growth factor β (TGFβ), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF I and II), β fibroblast growth factor (βFGF), epidermal growth factor, VEGF, and endothelial cell growth factor.[20] These various growth factors stimulate angiogenesis, epithelialization, granule tissue formation, extracellular matrix formation, and differentiation of cells.[25]

The main function of IGF-I in inflammation and healing is thought to be in migration and multiplication of fibroblasts, which leads to collagen and extracellular matrix protein synthesis.[26] Although IGF-I is present in all phases of healing and repair, it is most prominent during inflammation and proliferation.[26] Molly and colleagues[26] referenced a study by Sciore and colleagues, who demonstrated an increase of IGF-I and its receptor in rabbit medial collateral ligaments 3 weeks after injury. In transected Achilles tendon of rats, exposure to recombinant IGF-I resulted in improved healing starting 24 hours after injury/exposure to IGF-I, which lasted for 15 days.[27]

The widespread effects of TGF-β include mitosis control, activation and differentiation of mesenchymal stem cells, production and secretion of collagen, migration of endothelial cells, and angiogenesis.[21] TGF-β appears to have a large presence immediately following injury.[26] A study of flexor tendon cells showed that lactic acid, a substance that builds in early response to tissue hypoxia, stimulates TGF-β.[28] Research shows increased levels of TGF-β in the patellar ligament of rats up to 8 weeks after injury.[26] As cited in Molly and colleagues,[26] murine Achilles tendons exposed to cartilage-derived morphogenic protein 2, a growth factor in the TGF-β superfamily, had increased thickness and density in comparison with controls.

Another function of TGF-β1 is in fibrotic differentiation of skeletal muscle.[29] In vitro stimulation of myoblasts with TGF-β1 resulted in a further increase of the cytokine, production of proteins that regulate fibrosis, and formation of scar tissue in murine skeletal muscle.[30]

PDGF is found early in inflammation and stimulates production of growth factors such as IGF-I, in addition to remodeling of tissue.[26] Molly and colleagues[26] reviewed an in vivo study of rat medial collateral ligaments which showed that exposure to PDGF increased the strength, stiffness, and energy required to break the ligament.

The main function of VEGF is angiogenesis.[26] Contrary to previously discussed growth factors, which are most active during the inflammatory phase of healing and repair, VEGF levels are highest in the later phases.[26] As reviewed in Molly and colleagues,[26] VEGF was shown to increase the length and density of vessels in the flexor tendons of canines, from days 3 to 21 after injury.

βFGF plays a key role in angiogenesis, cell proliferation, and migration.[26] An article by Chan and colleagues, reviewed by Molly and colleagues,[26] showed an increase in type III collagen and cellular proliferation with varying doses of βFGF injected into damaged patellar tendons of rats (**Table 2**).

Table 2
Growth factors released from α granules of platelets, and their mechanism of action

Growth Factors Released from α Granules of Platelets	Action
Transforming growth factor β	Mitosis control, activation and differentiation of mesenchymal stem cells, production and secretion of collagen, migration of endothelial cells, angiogenesis, and fibrotic differentiation of skeletal muscle
Platelet-derived growth factor	Stimulates production of growth factors such as IGF-I, in addition to remodeling of tissue
Insulin-like growth factor I (IGF-I)	Migration and multiplication of fibroblasts, which leads to collagen and extracellular matrix protein synthesis
β Fibroblast growth factor	Angiogenesis, cell proliferation, and migration
Vascular endothelial growth factor	Angiogenesis

PRP and muscle

Some animal studies support the use of PRP in muscle strain. Hammond and colleagues[31] looked at the effect of PRP versus platelet-poor plasma on 2 different types of muscle strain, and found that the strain injuries from multiple light strains, previously shown to heal by myogenesis,[30] had better progress and faster return to full function compared with single heavy strain, which repairs by different means.[31] Myogenesis in those treated with PRP was also demonstrated by a significant increase in the number of central nucleated muscle fibers.[31] These central nucleated fibers are generally recognized as an indicator of muscle regeneration.[31] A potential obstacle in achieving healing of muscle tissue with PRP is the presence of TGF-β1, a profibrotic cytokine. Terada and colleagues[32] discovered that PRP and losartan, a TGF-β1 antagonist, provided skeletal muscle healing with minimal fibrosis in a murine model. Despite such promising findings, evidence regarding the clinical utility of PRP on muscle strain is mostly limited to case reports. Therefore, the clinical usefulness of PRP remains uncertain until more high-quality trials with adequate power are performed.

PRP and tendons

The utility of PRP for tendinosis at various anatomic locations has been examined in recent years, with varying results. Finnoff and colleagues[33] conducted a retrospective study on the effect of ultrasound-guided needle tenotomy followed by PRP on chronic tendinosis. The postprocedure ultrasound characteristics were evaluated prospectively. There was a 68% benefit in overall function and 58% improvement in worst-pain an average of 14 months after treatment. Follow-up ultrasonography showed improved echotexture in addition to fewer calcifications and neovessels. In a multicenter, retrospective survey study of PRP, Mautner and colleagues[34] examined patient satisfaction and perceived improvement for various chronic tendinopathies (most commonly lateral epicondyle Achilles and patella tendon). In this study population, there was an average reduction in visual analog scale (VAS) for pain of 74% (7.0 ± 1.8 to 1.8 ± 2). Eighty-five percent of patients were satisfied with their PRP treatment, with 82% reporting "moderate (>50%) to complete" improvement of symptoms at an average of 15 months after the injection. In general, PRP appears to be of benefit for tendinosis, although specific individual tendons achieve a better response (see later discussion).

Rotator cuff In recent years, multiple investigators have evaluated the efficacy of PRP for rotator cuff disorder. Some have studied the ability of PRP to augment the healing of operative rotator cuff repairs,[35–37] whereas others have looked at PRP as a direct treatment for rotator cuff injuries.[38,39] In a prospective, randomized, double-blind study, Weber and colleagues[35] compared recovery from arthroscopic rotator cuff repair with and without application of a platelet-rich fibrin matrix. There were no differences in range of motion, pain, and rate of retear at multiple time points up to 12 weeks postoperatively. In a prospective cohort study, Jo and colleagues[36] found that PRP did not enhance healing from arthroscopic rotator cuff repair in terms of discomfort, strength, movement, function, and satisfaction after 16 months. Similarly, Bergeson and colleagues[37] were unable to show the benefits of a platelet-rich fibrin matrix for arthroscopic rotator cuff repair in comparison with controls. Kesikburun and colleagues[38] compared PRP with saline for the treatment of chronic rotator cuff tendinopathy. There was significant improvement in both groups, with sizeable improvements in both pain and function. All patients underwent a 3-week therapy program 2 days following the injection. There was no difference in discomfort, mobility, quality of life, and disability between the 2 groups.[38] Rha and colleagues[39] compared ultrasound-guided PRP injection with dry needling. Dry needling or 2 PRP injections were performed 4 weeks apart. In contrast to the other studies, there was significant improvement in the Shoulder Pain and Disability Index scores, passive internal rotation, and flexion of patients treated with PRP as early as 6 weeks, which continued until 6 months postinjection. Although the utility of PRP for augmenting postoperative healing may be dubious, there seems to be a role for nonoperative management of rotator cuff tendinopathy.

PRP and the knee

Patellar tendon In a case series of 20 athletes with patellar tendinosis, Kon and colleagues[40] evaluated the effects of a series of 3 PRP injections, each given 15 days apart. The subjects had significantly improved overall function, pain, perception of physical and emotional health, vitality, and a sense of limitation at 6 months.[40] James and colleagues[41] looked at the utility of 2 injections of autologous blood at 4-week intervals, in combination with dry needling. The procedure resulted in significant improvement in the Victorian Institute of Sports Assessment score at follow-up, which averaged approximately 15 months.

Meniscus Ishida and colleagues[42] showed the regenerative properties of PRP on meniscal cells in vitro. The same study demonstrated that in vivo PRP combined with a hydrogel significantly improved healing of surgically produced meniscal lesions in a rabbit model.

Anterior cruciate ligament Murray and colleagues[43] showed that placement of a collagen-PRP framework after central anterior cruciate ligament (ACL) transection and suture repair stimulated healing of ACL as evidenced by histology and biomechanics in pigs.

PRP and Achilles tendon

A randomized, placebo-controlled trial by de Vos and colleagues[44] comparing PRP with saline injection failed to show the benefits of PRP for chronic Achilles tendinopathy after 24 weeks. Both interventions provided statistically significant improvement compared with baseline in terms of pain and level of activity, based on Victorian Institute of Sports Assessment Score A. All patients participated in a standardized therapy program consisting of eccentric loading exercises. However, the difference between

the PRP and control groups was not meaningful. On the other hand, Sanchez and colleagues[45] looked at the ability of platelet-rich fibrin to enhance healing of surgically repaired Achilles tendon ruptures. Patients who received the platelet-rich fibrin had improved ankle motion, with faster return to gentle running and sport. Moreover, subjects treated with platelet-rich fibrin returned to preinjury activity levels at a mean interval of 14 weeks, an average of 8 weeks earlier than controls.

PRP and the elbow complex

Ulnar collateral ligament Podesta and colleagues[46] reported the efficacy of PRP for partial ulnar collateral ligament tears in a case series of 34 athletes. Athletes returned to sport after a mean of 12 weeks. In addition, there was a statistically significant improvement in the mean Kerlan-Jobe Orthopedic Clinic Shoulder and Elbow score, and Disabilities of the Arm, Shoulder, and Hand score (DASH) at an average of 70 weeks after treatment. The mean elbow joint-space laxity on valgus stress also improved at follow-up.

Medial and lateral epicondylosis Creaney and colleagues[47] compared PRP and autologous blood injection for tennis elbow resistant to conservative management. Both methods offered significant benefit for pain and function; however, the differences between the interventions were negligible. A similar study of tennis elbow showed statistically significant improvement of the VAS pain score in favor of PRP, compared with autologous blood injection 6 weeks after treatment.[48] Mishra and Pavelko[49] reported the efficacy of PRP 8 weeks after treatment, in comparison with bupivacaine and epinephrine, for chronic elbow tendinosis. The Mayo elbow score and VAS pain score was used to assess outcome. In a randomized controlled trial, Krogh and colleagues[50] compared the effects of saline, glucocorticoid, and PRP on chronic lateral epicondylitis. No significant differences were observed between the groups 3 months after treatment, although patients who received steroid injection reported improved pain compared with saline and PRP 4 weeks following treatment. The investigators concluded that PRP and steroid injections did not result in better recovery when compared with saline injections, although steroid offered benefit in the short term. The potential long-term clinical benefits of PRP were elucidated by a randomized controlled trial by Peerbooms and colleagues.[51] PRP was compared with a corticosteroid injection using VAS pain score and DASH as primary outcomes. A 25% improvement in either score was defined as treatment success. At 4 weeks, patients treated with corticosteroids did better than those with PRP. As time passed, patients treated with PRP started to improve more than those who received steroids. By the time 6 months had passed, there was a meaningful improvement in PRP patients in comparison with those on steroids. This trend continued for up to 1 year. An interesting point is that those treated with corticosteroids, although showing improvement in the short term, started to decline, with minimal improvement at 6-month and 1-year follow-up. The benefits were sustained up to 2 years after treatment, which was shown in a continuation study by Gosens and colleagues.[52]

PRP and osteoarthritis

Osteoarthritis is degenerative in nature, and results from wear of articular cartilage and fibrocartilagenous structures. Growth factors play a role in monitoring the development and maintaining stability of articular cartilage, resulting in a growing interest in PRP as a potential treatment modality. Recent research regarding the utility of PRP in osteoarthritis has been promising. In the laboratory, PRP releasate was shown to reduce the numerous inflammatory effects of interleukin-1β in human chondrocytes.[53] Moreover, Akeda and colleagues[54] demonstrated a statistically significant increase in

chondrocyte DNA and collagen synthesis of chondrocytes treated with PRP in comparison with platelet-poor plasma or fetal bovine serum in a porcine model.

In human trials, several case series and cohort studies have shown favorable outcomes of PRP in the treatment of osteoarthritis of the knee.[55] In a prospective case series, Harpern and colleagues[56] found that a cohort of patients with grade I to III osteoarthritis (Kellgren-Lawrence radiographic classification) had better pain, function, and stiffness 6 months and 1 year following PRP.[56] Similar results were obtained in mild to severe osteoarthritis with 2 injections of PRP, 4 weeks apart, at 6 months and 1 year in terms of pain, function, and activity level. A prospective cohort study found that an intra-articular injection of PRP reduced VAS pain scores 6 months following the injection.[57] Increasing age, disease severity, and patellofemoral disease was associated with poorer outcomes. Sampson and colleagues[58] found an upward trend in the relief of pain and symptoms over 1 year in patients treated with a series of PRP injections every 4 months.

The benefits of PRP are also shown in multiple studies comparing PRP with hyaluronic acid (HA) injections. Cerza and colleagues[59] conducted a randomized controlled trial of 4 weekly injections of PRP with HA for grade I to III osteoarthritis (Kellgren-Lawrence radiographic classification). Although overall data showed a superior clinical outcome measured by the Western Ontario and McMaster (WOMAC) score at 4, 12, and 24 weeks, patients with grade III disease did not obtain significant benefit until 12 weeks after treatment. Similarly, in a prospective cohort study by Spakova and colleagues,[60] a series of 3 intra-articular PRP injections significantly improved WOMAC scores after 3 and 6 months in comparison with HA. A retrospective cohort study comparing PRP with HA found a statistically significant improvement in PRP 5 weeks after treatment.[61] Lastly, a prospective cohort study comparing a series of 3 intra-articular injections of PRP, low molecular weight HA, and high molecular weight HA discovered no difference between low molecular weight HA and PRP 2 months after treatment.[62] However, after 6 months, patients treated with PRP were meaningfully improved compared with both types of HA. The investigators observed that outcomes from PRP were similar to those after low molecular weight HA in older patients and worse disease, but were improved in younger subjects with milder disease.[62]

Stem Cells

The most recent and, perhaps, most exciting area of regenerative biological treatments is the use of mesenchymal stem cells in the treatment of various orthopedic conditions. There are various sources of stem cells that have been used for a variety of medical conditions, ranging from embryonic stem cells to human adult stem cells. Embryonic stem cell therapy is subject to significant regulatory and religious issues with potential adverse effects, with no studies supporting its use for orthopedic conditions. Human adult stem cells are available from various tissues including blood, adipose, bone marrow, and synovial tissue. The literature would support bone marrow as the main source and having most published research for orthopedic conditions. Harvesting mesenchymal stem cells (MSCs) from bone marrow is also associated with a lower complication rate in comparison with adipose-derived stem cell extraction. The multipotent nature of MSCs allows them to differentiate into various cells in the mesenchymal lineage, including bone, cartilage, adipose, and other soft tissues.[63]

At present, the literature supporting stem cell therapies for orthopedic conditions consists of some basic science and animal studies along with case reports, case series, and cohort studies in humans.[64]

Kuroda and colleagues[65] described the ability of MSCs to repair a 20 × 30 mm lesion of the medial femoral condyle in a Judo player. Seven months after treatment, the defect was filled with smooth tissue on arthroscopic evaluation. Biopsy of the tissue consisted of layers of fibrous tissue, hyaline-like cartilage, and chondral bone. Imaging studies also displayed filling of the defect, although a minor flaw was still detectable. Symptoms improved dramatically, and the patient resumed the previous level of athleticism. Similar findings were reported by Centeno and colleagues[66] for knee and hip osteoarthritis.[67] The investigators reported that magnetic resonance imaging (MRI) confirmed thickening of cartilage within the hip joint, in addition to resolving bone spur in severe hip osteoarthritis 4 weeks after injection of MSCs in a PRP scaffold.[67] The same group showed thickening of the meniscus and cartilage in a case of knee osteoarthritis at 24 weeks.[68] The patient reported significantly better pain and range of motion.

In addition, there have been case reports from the Regenexx Center regarding the effectiveness of stem cell treatments for patients who have suffered nonretracted ACL tears, with improvement noted clinically and on posttreatment MRI.

A case series of 6 female patients with severe knee osteoarthritis who received intra-articular mesenchymal stem cell injections showed improvement at 6 months and 1 year.[68] The VAS pain score, WOMAC index, and walking distance showed steady improvement until 6 months, followed by a slight decline at 1 year. Repeat MRI evaluation at 6 months showed thicker cartilage and smoother chondral surfaces. A cohort of 30 patients (≥65 years) with knee osteoarthritis underwent arthroscopic lavage and injection of adipose-derived stem cells under arthroscopic guidance.[69] Subjects were followed for 2 years. There was a significant decrease in VAS score at 2 years, and an increase in the Knee Injury and Osteoarthritis Outcome Score at all points of follow-up (3 months, 1 year, and 2 years). Long-term healing was demonstrated by significant improvement in clinical parameters from 1 to 2 years of follow-up. After 2 years, 16 subjects underwent repeat arthroscopy. Compared with baseline, 87.5% had preservation or improvement of the appearance of cartilage. At present there are no prospective, randomized controlled trials with adequate power to elucidate the true clinical value of stem cell therapy. Regenexx has now collected registry data from its multiple centers throughout the United States using a standardized approach to extraction and delivery of bone marrow stem cell therapy for a variety of orthopedic conditions, which includes: osteoarthritis of the shoulder, hip, and knee; meniscal tears of the knee; avascular necrosis of the hip; rotator cuff tears; Achilles tendon tears; and ACL tears. A stratification of patients was performed at the time of these procedures with patients classified as being good, fair, or poor candidates based on a variety of factors including the patient's age, comorbidities, body mass index, activity level, severity of the condition, and so forth, to better determine which patient type best responds to stem cell therapy. The data from this registry have demonstrated that more than 90% of these patients had at least some level of improvement, with those rated good candidates showing 55% to 60 % improvement in pain and function; fair candidates improving on average 45% to 50%, and poor candidates improving by approximately 35%. Recent results from this registry have demonstrated a durability of up to 3 years for these improvements. In addition, in case reports of fluoroscopically placed bone marrow stem cells, there is evidence of healing of partial ACL tears and nonretracted rotator cuff tears on serial MRI (see Regenexx.com.)

Although this area of treatment remains exciting and with great potential, more rigorous research is necessary before any reliable conclusions can be made regarding the role of stem cell therapy in the treatment of severe tendon and cartilage pathologies.

SUMMARY

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. These treatments, in conjunction with aggressive/comprehensive rehabilitation, may maximize the nonsurgical treatment of these various sports injuries. This review is by no means a complete review of the literature. There is currently level-1 evidence to support the use of PRP for tendinopathies of the elbow complex and osteoarthritis of the knee. Additional studies appear to demonstrate efficacy in other tendons and ligaments. Although some reports have shown effectiveness, stringent medical evidence is lacking for the use of prolotherapy and stem cell therapy, in addition to PRP for muscle strain, most ligamentous sprains, patellar tendinosis, Achilles tendinosis, and rotator cuff injuries to a certain extent. 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.

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