PM R 7 (2015) S33-S40

www.pmrjournal.org

Regenerative Medicine

Where Do Injectable Stem Cell Treatments Apply in Treatment of Muscle, Tendon, and Ligament Injuries?

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Abstract

Treatment options for muscle, tendon, and ligament injuries span a constantly evolving spectrum. For years, treatments focused on symptomatic relief. Closer scrutiny of symptomatic treatment suggests that the provision of transient relief of symptoms may have caused more harm than good. Cortisone injections provide a trade-off of short-term relief for poorer long-term outcomes. When conventional treatment failed, patients have faced limited options including surgery, which has increased risk and limited efficacy. Regenerative injections offer a more robust option for soft tissue disease. Basic science and clinical studies show conflicting results to support the use of platelet-rich plasma injections for soft tissue disorders, and even fewer trials have focused on injectable stem cells with limited findings. Additional studies are needed to determine the potential benefits of this regenerative therapy.

Introduction

The algorithm for treatment of muscle, tendon, and ligament injuries continues to evolve. At its core, the pathology of these injuries boils down to an increase in physiologic demand that overwhelms structural integrity. Traditional treatment paradigms focus on trials of symptomatic management with a reduction in the offending activity [1]. As musculoskeletal tissue injuries become chronic, the effectiveness of current therapies wanes. Previously, many patients were left with limited options beyond coping with persistent pain and reduced function or a possible surgery with modest outcomes.

Advances in our understanding of the pathophysiology of tendon, muscle, and ligament injuries, together with evolving research in regenerative therapies, may alter our treatment algorithm. The role of orthobiologics in the treatment of musculoskeletal tissue disease could potentially fill a void in the spectrum of treatment options. Currently, however, data are conflicting regarding the use of platelet-rich plasma (PRP) injections to treat soft tissue disorders, and no stem cell technologies have been approved by the Food and Drug Administration (FDA) for the treatment of degenerative musculoskeletal conditions [2]. It is clear that further studies are needed to explore the effectiveness of stem cell therapy and its role as the next generation of orthobiologics.

Injection Therapies for Soft Tissue Injury

Current injection therapy options for soft tissue injuries include corticosteroids, prolotherapy, percutaneous needle tenotomy, PRP, and variations on injectable stem cells.

Corticosteroids

Corticosteroids have historically been the most widely used injection therapy for muscle, tendon, and ligament injury [3]. Although they provide some short-term analgesia, corticosteroids may inhibit collagen synthesis and decrease tendon strength [4]. A systematic review of more than 40 randomized, controlled trials for corticosteroid injections published in *Lancet* in 2010 noted that these injections provide short-term pain relief but that these effects were reversed at intermediate and long terms. It was also noted that patients treated with corticosteroid injections had worse outcomes than did persons who did not receive an injection [5]. In a placebo-controlled study published in *JAMA* in 2013, 165 patients with at least a 6-week

1934-1482/$ - see front matter
http://dx.doi.org/10.1016/j.pmrj.2014.12.012

history of lateral epicondylosis were randomized into 4 groups—2 involving corticosteroid injection, with or without physical therapy and 2 involving placebo injection, with or without physical therapy. Participants who received a corticosteroid injection had worse clinical outcomes and higher rates of recurrence at 1 year compared with participants who received a placebo [6]. One randomized controlled trial and one cohort study examining the effects of corticosteroid injections on Achilles tendonitis showed no benefit compared with placebo with regard to cure rate or healing times. Furthermore, a review of animal studies has demonstrated that these injections temporarily weaken the tendon if given intratendinously but have no effect on tendon strength if injected into the paratenon [7]. At best, corticosteroid injections provide short-term relief for soft tissue injuries. At worst, they lead to lower functional outcomes and higher recurrence of disease.

Prolotherapy

The use of prolotherapy dates to the 1930s [8], when it was developed for pain associated with presumed ligament laxity. Sclerosing agents such as hyperosmolar dextrose are the most popular and best-studied prolotherapy agents [9]. The theoretical basis of their efficacy is that irritant solutions along with needling of soft tissues stimulate a low-grade inflammatory reaction that initiates a healing cascade of the injured soft tissues. Multiple uncontrolled studies and case series have demonstrated effectiveness of prolotherapy in the treatment of musculoskeletal pain, including low back [10,11] , neck, and whiplash injuries [12]; chronic sprains and/or strains; tennis and golfer's elbow [13]; plantar fasciitis [14]; knee [15], ankle, and shoulder pain; and chronic tendinosis, including Achilles tendinosis [16,17]. Prolotherapy today remains an often-used treatment for chronic soft tissue injuries.

PRP

The first use of PRP dates back to 1987 following open-heart surgery [18]. Periodontal and wound healing were early successful clinical applications. By the 1990s, the use of PRP to accelerate healing gained acceptance in surgical circles. However, the machines were large, expensive, and only used in hospital operating rooms. By the 2000s, the machines were smaller and available for use in an office setting [19].

Platelets contain a significant number of key signal proteins, growth factors, chemokines, cytokines, and other bioactive factors that initiate and regulate the inflammatory cascade [20]. Elevated platelet concentrations are known to stimulate proliferation and differentiation of mesenchymal stem cells at an injury site [21], resulting in natural wound healing [22].

The role of PRP in sports medicine increased after Mishra and Pavelko [23] published a study noting its effectiveness in treatment of recalcitrant chronic lateral elbow tendinosis. Further studies have corroborated the efficacy of PRP in treatment of tendinosis [24,25] and ligament injury [26]. However, studies refuting the improved efficacy of PRP versus injection of saline solution have also been published. Most notably, a study by de Jonge et al in 2010 and their follow-up in 2011 demonstrated no added benefit of PRP versus saline solution for chronic mid-portion Achilles tendinopathy [27]. In a randomized controlled trial, an experimental group of 16 patients with Achilles tendon rupture who were injected with PRP was compared with a group of 14 patients who did not receive the PRP injection. Both groups underwent surgical repair, and no significant differences in functionality were found between the 2 groups as measured by a heel raise index and an Achilles Tendon Total Rupture Score [28]. A prospective randomized trial evaluating the use of PRP in anterior cruciate ligament (ACL) reconstruction showed no added benefit to ACL reconstruction alone with respect to inflammatory parameters (C-reactive protein), magnetic resonance imaging appearance of the graft, and clinical evaluation scores (KT-1000 arthrometer and visual analog scale) [29]. As treatment protocols become standardized, future research should elucidate the optimal use of PRP in soft tissue injures, whether chronic or acute.

Stem Cells

Whereas PRP acts to provide a favorable environment to recruit progenitor cells and stimulate healing of musculoskeletal tissues, stem cell therapy offers the possibility of directly injecting progenitor cells to the area of damage. By definition, stem cells are able to self-renew and exist in an undifferentiated or unspecialized state, and they are capable of differentiation or specialization along multiple lineages. Nascent stem cells exist within various adult tissues including bone marrow, brain, dermis, periosteum, skeletal muscle, synovium, trabecular bone, and vasculature [30].

Adult stem cells consist of 2 general classifications: hematopoietic stem cells, which are responsible for the formation of blood products, and mesenchymal stem cells (MSCs). In the early 1990s, adult MSCs were discovered to have an active role in connective tissue repair [31]. Since that time, impressive progress toward the development of safe clinical applications for MSC-mediated therapy has been achieved. It is now technically feasible to harvest tissue cells, culture them (if needed) to expand the cell population, and then inject these cells directly into areas of injury.

Several injectable stem cell therapies with differing cell origins now abound, including MSCs, tenocyte-derived stem cells, adipose-derived stem cells,