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Operative Techniques in
Orthopaedics

Clinical Outcomes of Biologic Treatment for Chronic Tendinopathy

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Biological interventions, such as ultrasound-guided platelet-rich plasma (PRP) injections, are a second-line treatment worth considering for recalcitrant tendinopathy, but efficacy and effectiveness have not been established yet. The use of PRP has been most commonly studied in lateral epicondylitis, with 9 randomized controlled trials and 7 prospective controlled studies in the medical literature. Corticosteroid injection was used as the comparator in 6 studies, autologous blood in 3, and local anesthetic agents in 2 studies. Recent meta-analyses showed that the PRP and autologous blood are superior to corticosteroids in pain reduction and ameliorating functionality in epicondylitis. PRP efficacy on supraspinatus tears is controversial, and PRP is better than controls in 2of 5 studies, when compared with corticosteroids and dry needling. Patellar tendinopathy is examined in 4 controlled studies and 8 case series, with PRP ameliorated outcomes but not in all cases. Whether more than 1 injection should be given is under discussion. Achilles tendinopathy was examined in 3 prospective controlled studies (a single injection) and 6 case series. Patients showed improvements regarding baseline values, but 2 controlled studies failed to reveal differences with controls. Pooling data across studies are challenging because of heterogeneity in outcome scores and comparators. Tendinopathy progression and outcomes are poorly monitored with self-reported questionnaires that are not sensitive enough to discriminate local changes. Molecular indicators of tendon health and disease can help to assess whether the condition progresses or heals after biological interventions. The international consensus about the design of clinical studies should be pursued.
Oper Tech Orthop 26:98-109

KEYWORDS platelet-rich plasma, clinical outcome, tendinopathy, tendon

Introduction

Tendinopathy is a chronic disease with progressive degeneration of extracellular matrix, microtearing, and loss of tendon microarchitecture as a hallmark. The essential pathologic lesion of tendinopaty is often described as a failed healing response of the tendon, and persistence of the lesion is attributed to the tissue anchored in the proliferative or angiogenic phase, as shown in histopathology. Failure in remodeling processes and tissue maturation is also reported by some other authors, as some tendons show mucoid, hyaline, and fibrous degeneration. During progressive tissue changes and deviation from tendon homeostasis, patients experience pain, tenderness, and functional limitations.[1]

There is much we do not know about the chronology of the tendinopathy trajectory. Currently, the temporal description of the process is based on typical healing stages, and depicted as an inflammatory phase, followed by a proliferative or angiofibroblastic stage, cell differentiation, and ECM remodeling and maturation.[2]

The contribution, to both repair and pathology, of exogenous and endogenous cells is acknowledged. Activated resident cells (ie, tenocytes and tendon progenitor cells), migratory cells, and peripheral fibroblasts are involved in repair and in the maintenance of homeostasis. In fact, local and migratory cells can modulate inflammation or angiogenesis, and

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http://dx.doi.org/10.1053/j.oto.2015.12.007
1048-6666//

synthesize or degrade ECM components. However, the functions of these cells during the course of progressive extracellular matrix degeneration have not been clarified.

It has been suggested that biological interventions, such as platelet-rich plasma (PRP) and cell therapies, can halt the progression of tendinopathy and can be included in the new developing field of orthobiologicals. Among biological therapies, PRP has expanded rapidly in orthopaedics and sports medicine. Because cells are the main players in repair mechanisms and homeostasis preservation, they are considered as main targets in PRP treatments.

PRP is defined as plasma with a platelet count above that of the peripheral blood from which it is obtained, most often by centrifugation. Its biological actions are chiefly attributed to the pool of growth factors and cytokines released from platelets along with plasma proteins. PRP modulate cell behavior; broadly, they influence cell differentiation, migration, the synthesis of ECM, inflammation, and angiogenesis.[3]

As an alternative biological intervention, mesenchymal cell therapies for tendon are being developed and can also be used in combination with PRP. Grafted cells, such as tenocytes and skin fibroblasts, participate in tissue repair using their trophic activities, that is, collagen synthesis, and also by modulating the immune response. However, these therapies are expensive, and there are few studies endorsing their efficacy.[4,5]

PRP injections are not expensive, and they have been implemented as a second-line intervention for tendinopathies. However, their efficacy is still debated, and a recent meta-analysis (including studies in various tendons) points toward a moderate effect of PRP in main clinical outcomes, that is, pain and functionality.[6] The efficacy of PRP has not been demonstrated yet in any tendinopathy,[7] but new clinical information is continuously emerging.

This is a narrative review updating clinical research in biological interventions, namely PRP injections. The goal is to provide a comprehensive overview of current clinical information available in the medical literature for tendinopathies treated with PRP. Recent meta-analyses concerning the clinical efficacy of PRP are also discussed.

Methods

Search for Clinical Data

We searched PubMed, Web of Science, and OVID with combinations of the following search terms: "platelet-rich plasma," "tendon," "rotator cuff," "tendinitis," "tendinopathy," "epicondylitis," "Achilles," "patellar," "sports," and "human" from January 2003-September 2015. We also searched the authors' own files. We included only scientific articles published in English. All clinical studies examining the effects of conservative PRP interventions for tendinopathy, controlled and uncontrolled, were included. We excluded studies regarding PRP interventions during open surgery or arthroscopy. Conference proceedings and case reports were excluded. The review is also based on recent systematic reviews and meta-analyses.

From all selected clinical studies level of evidence, the type of participants, the type of interventions, types of outcome measures, and clinical outcomes were extracted and tabulated. We also describe whether the PRP formulation is classified as pure or leukocyte enriched.

The results were synthesized by grouping the studies based on anatomical locations, as main tendon lesions in the elbow and shoulder, and lesions in the patellar tendon and Achilles tendon. Additionally, when possible we have grouped controlled studies attending to comparators.

Results

Reports on the clinical use of PRP injections for tendinopathy have been published starting from about a decade ago.[8] At present, this is a very active research field. Although some consider PRP as an experimental treatment, PRP injections are widely used as a second-line intervention, chiefly when other conservative treatments have failed. Clinical efficacy is measured as if PRP were symptomatic intervention, that is, outcome instruments evaluate pain reduction and changes in functionality. Few studies analyzed changes in morphology using magnetic resonance imaging (MRI) or ultrasound. Histologic analyses are not provided in any study.

Elbow

Lateral epicondylitis (tennis elbow) is an enthesopathy of the common extensor origin at the humerus; it affects 1%-3% of a middle-aged population (35-54 years), and it is by far more common than medial epicondylitis (Golfer elbow).

In the PRP field, epicondylitis is the most investigated among tendinopathies. Currently, 9 randomized clinical trials[9-13,14-18] and 7 prospective case-control studies,[8,19-24] with a total of 618 patients in groups given PRP (and a total of 519 patients in control groups), have examined the likelihood that patients improve their functional status and experiment pain reduction. Uncontrolled studies include 2 case series[25,26] and a retrospective study[27]; however, without controls, benefits cannot be attributed to the treatment per se, particularly in epicondylitis that is a self-limiting condition in many cases.

Most of the studies included patients with chronic tendinopathies (more than 3-6 months of symptoms) that were nonresponsive to other conservative managements. The most common measurement instruments are patient self-reported questionnaires designed to appraise changes in pain and limitations in the performance of daily activities. In fact, it has been hypothesized that physiologic severity could be assessed by alterations in daily activities. Most commonly used questionnaires includethe following: patient-rated elbow evaluation; disabilities of the arm, shoulder, and hand (DASH); modified Mayo Clinic Performance Index for Elbow); and Oxford Elbow score. From these, DASH is the most validated score to other common languages, that is, Spanish, Italian, etc.

Table 1 shows clinical studies tabulated according to the comparators used in the control group. Although there is no