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Mini Review

Use of Hyaluronic Acid for Rotator Cuff Tendinopathy

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Introduction

The tendon healing process is slow and structured in multiple phases, from inflammatory cytokine recruitment to growth factors and reparative cell involvement. As a result of the healing process, it is widely known that there is the frequent formation of inferior quality fibrotic scar tissue or fibrous adhesions, which modify the structure and function of the tendon. Beyond preventive measures, therapeutic strategies in the case of persistent lesions include biomechanical corrections, anti-inflammatory drugs, instrumental therapies such as shock wave or electromagnetic field stimulation, and recent regenerative stimulation therapies. These regenerative therapies such as hyaluronic acid (HA), platelet-rich plasma (PRP), or growth factors (GFs) aim to stimulate an anabolic environment. It is important to recall that some tendon lesions are require surgical treatment according to the tear type, and in this setting, the role of regenerative therapies would be to enhance the operative results.

Hyaluronic Acid in Tendons

Several studies have proved that hyaluronic acid peritendinous infiltration can improve symptoms and function in patients with rotator cuff disorders. This fact is interesting because it is a fast, safe, and minimally invasive procedure and does not have the deleterious side effects of NSAIDs or cortisone injections, which have adverse effects in tendon healing, favoring catabolic activity and often are contraindicated in elderly patients with comorbidities such as diabetes or hypertension [1,2].

Hyaluronic acid is composed of repeating disaccharide units of N-acetyl-D-glucosamine and D-glucuronic acid, linked by alternating β_{1-3}, and β_{1-4}. It is found in most connective tissues and is mainly concentrated in synovial fluid, the eye's vitreous fluid, where it helps to maintain viscosity [3]. It is naturally synthesized by a class of integral membrane proteins called hyaluronan synthases and degraded by a family of enzymes called hyaluronidases. Its structure conserved in all animals that HA is present, which explains the good levels of biocompatibility of highly purified HA.

Hyaluronic acid action in tissues varies depending on its composition; for example, high molecular weight hyaluronic acid has the immunosuppressive capacity, thus decreases inflammatory reaction, apoptosis, and angiogenesis, and by this means it decreases pain [4,5]. On the other hand , low-weight molecular chains have a pro-inflammatory effect, with the secretion of cytokines and stimulation of angiogenesis [4,6]. Thus, according to the desired treatment, careful selection must be made regarding the desired outcomes. In our experience, we use middle-weight hyaluronic acid to profit from both benefits; to stimulate regenerative healing potential and to relieve pain and cell damage produced by the inflammatory process.

Middle-weight and low-weight hyaluronic acid have been tested for epidermal growth, and they have proved to stimulate tissue regeneration in comparison to control, with more rapid and effective healing. It has also been shown to decrease the oxidative reaction effect that usually occurs when a negative external factor damages the tendon. Its action is achieved by inhibiting redox reaction and TNF- α, thus increasing cell viability and providing a pro-anabolic environment [7]. Reactive oxygen species (ROS) can easily degrade hyaluronic acid; for this reason, newer molecules have been developed as stabilizers to prevent hyaluronidase digestion, such as trehalose or nicotinamide, among others. These stabilizer molecules are being investigated as they have a positive role by helping in decreasing the ROS cascade and thus decreasing the noxious inflammatory action [8,9].

Regarding its application for tendinopathies, hyaluronic acid has proven to have cytoprotective effects in tenosynovitis, as shown

by the study of *F Salamanna, et al.* [10], were repeated peri patellar injections of hyaluronic acid in detrained rats, and demonstrated to maintain the anabolic activity of the tenocytes.

In vivo clinical application for tendinopathies has proven to be safe and provides significantly improved clinical outcomes compared to placebo when applied peritendinous in Achilles tendinopathy [11] and rotator cuff tears. Four studies [12-15] comparing patients undergoing HA versus phosphate-buffered saline injections reported good clinical results and pain relief. In particular, Blaine [13] showed better ROM recovery, reduced pain at night, and significantly higher overall satisfaction in the HA group; Meloni [12] showed a significant difference in the improvement of clinical symptoms and recovery of functional status in patients at one month after the end of the HA infiltrative cycle, in particular HA group VAS score was 2.8 respect 8.0 in the sodium chloride solution group.

We developed an observational prospective non-controlled study regarding this positive clinical evidence. The study analyzes the clinical outcomes and the safety of middleweight hyaluronic acid plus a nicotinamide stabilizer agent for treating rotator cuff tendinopathy. The infiltrations are applied peritendinous and in an echo-guided fashion. Selected patients are those with persistent pain, more than three months, meaning that self-healing potential was limited, aging from 18 to 65 years, with six months of follow-up. So far, preliminary results are promising, showing a considerable reduction in VAS score and an improvement in OXFORD shoulder scores at the first six weeks compared to baseline, as well as no adverse events have been reported. However, there is still more follow-up needed in order to obtain further conclusions.

Conclusion

Rotator cuff tendinopathy is a frequent problem that, according to the type of tear and patient characteristics, often can present fibrous scar tissue, with low healing potential, and a slow, painful healing process. Here, hyaluronic acid appears as a less invasive treatment, capable of enhancing anabolic tendon healing potential and decreasing inflammatory nocive cascade. By this means, we aim to use newly available technologies, decrease NSAID consumption or corticoid injections, and prevent further tendon deterioration, thus optimize the healing process, and improve articular function.

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