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Autologous Growth Factor Injections in Chronic Tendinopathy

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Reference: de Vos RJ, van Veldhoven PLJ, Moen MH, Weir A, Tol JL. Autologous growth factor injections in chronic tendinopathy: a systematic review. *Br Med Bull*. 2010;95:63–77.

Clinical Question: The authors of this systematic review evaluated the literature to critically consider the effects of growth factors delivered through autologous whole-blood and platelet-rich–plasma (PRP) injections in managing wrist-flexor and -extensor tendinopathies, plantar fasciopathy, and patellar tendinopathy. The primary question was, according to the published literature, is there sufficient evidence to support the use of growth factors delivered through autologous whole-blood and PRP injections for chronic tendinopathy?

Data Sources: The authors performed a comprehensive, systematic literature search in October 2009 using PubMed, MEDLINE, EMBASE, CINAHL, and the Cochrane library without time limits. The following key words were used in different combinations: *tendinopathy*, *tendinosis*, *tendinitis*, *tendons*, *tennis elbow*, *plantar fasciitis*, *platelet rich plasma*, *platelet transfusion*, and *autologous blood or injection*. The search was limited to human studies in English. All bibliographies from the initial literature search were also viewed to identify additional relevant studies.

Study Selection: Studies were eligible based on the following criteria: (1) Articles were suitable (inclusion criteria) if the participants had been clinically diagnosed as having chronic tendinopathy; (2) the design had to be a prospective clinical study, randomized controlled trial, nonrandomized clinical trial, or prospective case series; (3) a well-described intervention in the form of a growth factor injection with either PRP or autologous whole blood was used; and (4) the outcome was reported in terms of pain or function (or both).

Data Extraction: All titles and abstracts were assessed by 2 researchers, and all relevant articles were obtained. Two researchers independently read the full text of each article to determine if it met the inclusion criteria. If opinions differed on suitability, a third reviewer was consulted to reach consensus. The data extracted included number of participants, study design, inclusion criteria, intervention, control group, primary outcome measures (pain using a visual analog or ordinal scale or function), time of follow-up, and outcomes for intervention and control group (percentage improvement) using a standardized data-extraction form. Function was evaluated in 9 of the 11 studies using (1) the Nirschl scale (elbow function) or the modified Mayo score for wrist flexors and extensors, (2) the Victorian Institute of Sports Assessment-Patella score, a validated outcome measure for patellar tendinopathy, or the Tegner score for patellar tendinopathy, and (3) the rearfoot score from the American Orthopaedic Foot and Ankle Scale for plantar fasciopathy.

The Physiotherapy Evidence Database (PEDro) scale contains 11 items; items 2–11 receive 1 point each for a *yes* response. Reliability is sufficient (0.68) for the PEDro scale to be used to assess physiotherapy trials. A score of 6 or higher on the PEDro scale is considered a high-quality study; below 6 is considered a low-quality study. The PEDro score results determined the quality of the randomized controlled trial (RCT), nonrandomized clinical trial, or prospective case series ($\geq$6 or $<$6). A qualitative analysis was used with 5 levels of evidence (strong, moderate, limited, conflicting, or no evidence) to determine recommendations for the use of the intervention. The number of high-quality or low-quality RCT or nonrandomized clinical trial studies with consistent or inconsistent results determined the level of evidence (1–5).

Main Results: Using the specific search criteria, the authors identified 418 potential sources. After screening of the title or abstract (or both), they excluded 405 sources, which left 13 studies. After viewing the full text, they excluded 2 additional sources (a case report and a study in which the outcome measure was remission of symptoms and not pain or function), leaving 11 studies for analysis. Six of the 11 studies were characterized by an observational, noncontrolled design; the remaining 5 studies were controlled clinical trials, 2 of which had proper randomization.

The mean number of participants included in the studies was 40.5 (range = 20 to 100). Three of the studies were on "tennis elbow," 1 on "golfer's elbow," 1 on wrist extensor or flexor tendinopathy, 3 on plantar fasciopathy, and 3 on chronic patellar tendinopathy. Based on the information reported, there was no standardization of frequency or method of growth factor injection treatment or of preparation of the volume, and an optimal mixture was not described. Autologous whole-blood injections were used in 8 studies; in 5 studies, the autologous whole-blood injection was combined with a local anesthetic. In contrast, a local anesthetic was used in only 1 of the 3 PRP injection studies. The authors of the other 2 studies did not report whether a local anesthetic was used. The number of autologous whole-blood and PRP injections varied, ranging from 1 to 3. The centrifuging process was single or double for the PRP injections. In 2 studies, calcium was added to activate the platelets. A visual analogue or ordinal pain scale was used in 10 of the 11 studies. Function was evaluated in 9 of the 11 studies using (1) the Nirschl scale in 4 elbow studies or the modified Mayo score at baseline in 1 elbow study, (2) the Victorian Institute of Sports Assessment-Patella score for 1 study and the Tegner score for 2 of the patellar tendinopathy studies, and (3) the rearfoot score of the American Orthopaedic Foot and Ankle Scale for 1 plantar fasciopathy study. Only 1 study used an appropriate, disease-specific, validated tendinopathy measure (Victorian Institute of Sports Assessment-Patella).

All intervention groups reported a significant improvement in pain or function score (or both), with a mean improvement of 66% over a mean follow-up of 9.4 months. The control groups in these studies also showed a mean improvement of 57%. None of the pain benefits among the intervention groups were greater than those for the control group at final follow-up. In 4 of the studies, the control group and the autologous growth factor

injection group had similar results in pain or function or both, whereas in 2 studies, the control group had greater relief in pain than the injection group.

Eleven studies were assessed using the PEDro scale. The PEDro scores for these studies ranged from 1 to 7, with an average score of 3.4. Only 3 studies had PEDro scores of $\geq$6 and were considered high quality. The 3 high-quality plantar fasciopathy studies used autologous growth factor injections but did not show a significant improvement over the control group. One of the studies that showed no beneficial effect for the autologous growth factor injections was compared with corticosteroids. Compared with other treatments, level 1 (strong) evidence demonstrated that autologous growth factor injections did not improve pain or function in plantar fasciopathy. The PRP injection results were based on 3 low-quality studies, 2 for the patellar tendon and 1 for the wrist flexors-extensors; level 3 (limited) evidence suggests that PRP injections improve pain or function.

Conclusions: Strong evidence indicates that autologous growth factor injections do not improve plantar fasciopathy pain or function when combined with anesthetic agents or when compared with corticosteroid injections, dry needling, or exercise therapy treatments. Furthermore, limited evidence suggests that PRP injections are beneficial. Except for 2 high-quality RCT studies, the rest were methodologically flawed. Additional studies should be conducted using proper control groups, randomization, blinding, and validated disability outcome measures for pain and function. Until then, the results remain speculative because autologous whole-blood and PRP injection treatments are not standardized.

Key Words: tendon injuries, platelet-rich plasma, injection therapy

COMMENTARY

Tendinopathy is becoming more common in sporting, recreational, and work-related activities because of the number of participants and increases in activity level.[1,2] Although historically more common in the population older than age 40, now a greater percentage of younger athletes experiences tendon pain.[3] Symptoms of tendinopathy may include persistent pain, loss of range of motion, and dysfunction that can prevent a return to full activity.[2] Furthermore, with a chronic connective tissue disorder, regeneration does not occur, resulting in a tissue structure that may incur further injury or rupture due to a failed healing repair response.

When the traditional rehabilitation programs of exercise augmented with modalities or manual therapy alone fail or athletes become noncompliant,[2] other methods are considered.

At this point, clinicians and athletes may find themselves contemplating alternative therapy in conjunction with rehabilitation or surgery. Although eccentric muscle-training programs for patellar, Achilles, and elbow-extensor tendinopathy have been shown to be effective,[1,2] 12 weeks are required for successful treatment. As clinicians consider alternative interventions to use in conjunction[3,4] with rehabilitation for chronic tendinopathy, including corticosteroids, dry needling, extracorporeal shockwave therapy, and autologous growth factor injections, the time required for successful treatment needs to be recognized because an alternative treatment may not be effective overnight. A critical mass of good literature supports some of these interventions. However, other studies are of poor methodologic quality; have high dropout rates based on the length of treatment, which results in limited long-term follow-up; or showed that the control group improved more than the experimental treatment group.

In their systematic review, de Vos et al[5] provided a qualitative analysis of growth factor injections with whole blood and platelet-rich plasma (PRP). They concluded that growth factor injections should not be recommended because autologous blood injection for plantar fasciopathy is not superior to other treatments, and limited evidence indicates that PRP injections may be beneficial. Moderate to little evidence was noted in other systematic reviews when PRP was compared with corticosteroids and other injections or with a placebo for tendon healing.[3] Moderate evidence was noted for only 1 high-quality randomized controlled trial (RCT) for lateral epicondylagia: pain and function improved more with corticosteroid treatment than with PRP in the short term, but in the long term, PRP was more effective in reducing pain. Sheth et al[4] noted that RCTs of PRP injection studies for Achilles tendinopathy and lateral epicondylitis and nonrandomized clinical trial studies for chronic elbow tendinosis and chronic refractory patellar tendinopathy were of very low quality. In RCTs and nonrandomized clinical trials, evidence for the use of autologous whole-blood injections in plantar fasciopathy was also of very low quality. Taylor et al[6] reported mixed results regarding the effectiveness of PRP treatment. Currently, more evidence is available to support the use of PRP in treating lateral elbow tendinosis than in treating Achilles and patellar tendinopathy and plantar fasciopathy.[6] These findings may require athletic trainers to be cautious about recommending these injections but do not justify dismissal of these injections as an ineffective treatment. Given that to date we have had more low-quality than high-quality studies evaluating the use of autologous whole-blood injections and PRP for tendon healing, we need more high-quality studies of the patient populations seen in the athletic training clinical setting. These may provide more evidence for athletic trainers and physicians to consider the use of autologous whole-blood or PRP treatments in this population.

Based on in vitro (cell cultures) and animal study results, autologous growth factor injections or PRP may affect collagen production and the degradation that follows by influencing "matrix-regulating enzymes."[7] Degranulation of the alpha granules in the platelets releases growth factors and proteins that reside in the granules. The granules contain cytokines that signal cells to express platelet-derived growth factor, transforming growth factor β, and vascular endothelial growth factor.[7] After the cytokines are released, they bind to local or circulating cells. Intracellular signaling is initiated, which results in the expression of proteins responsible for matrix synthesis and cell proliferation. Tissue regeneration through angiogenesis, extracellular matrix production, and collagen synthesis occurs.[7] Dense granules are also important as they contain adenosine (energy), serotonin (neurotransmitter), histamine (vasodilator), and calcium (for wound healing). However,

not all PRP preparations may be able to induce these pathways.

Although this mechanism of the effect of growth factors on tendon tissue is plausible, great variability exists in how PRP treatments are performed, which may lead to inconsistent clinical results. Of primary concern is the lack of standardization of frequency or method of growth factor injection treatment, preparation of the volume, or a description of the optimal mixture for injections of autologous growth factors using whole blood and PRP.[6] In preparing the concentrate, how long or how many times (single or dual) should the material be centrifuged or a cell-separating system used? What are the recommended volumes of platelets and leukocytes in the concentrate? How many injections are required? Should a local anesthetic, dry needling, or calcium be used to activate the platelets? With an increasing range of products available for production of PRP, it is unclear what levels of platelets, leukocytes, or growth factors the concentrate contains. Not all cell-separating systems eliminate leukocytes from the concentrate. A concentrate with leukocytes and platelets present may negate the healing response and lead to an increased catabolic rate of tissue destruction.[7] Given this variability and the lack of clinical trials in which platelets, growth factors, and other substances have been measured, it is difficult to determine optimal platelet and growth factor concentrations. Furthermore, our understanding of the complex nature of growth factor functions and interactions in PRP preparations remains in the early stages.

The differences in healing responses in load-bearing (Achilles and patella) and non–load-bearing tendons (wrist flexors and extensors) should be addressed. Within 1 year, recovery of wrist-extensor tendinopathy may be 80%–90%, as noted by deVos et al.[5] Achilles tendinopathy can consist of insertional or midsubstance degradation. These areas differ in biomechanics, metabolic properties, and responses to treatment.[8] Further, Combs et al[3] discussed the lack of generalizability between anatomical locations. Despite similar pathologic changes to tendons, subtypes of tendinopathy may not respond to autologous whole-blood or PRP injections. Hence, the results of high-quality RCTs studying autologous growth factor injections for plantar fasciopathy may not generalize to the wrist flexors and extensors or Achilles or patellar tendons.

Another problem with outcomes-based tendinopathy studies is that subjective pain scales may be used in addition to validated functional measures, which may not be specific to tendinopathy. Validated outcomes-assessment tools should be used to reflect the disease-specific treatment response. In the review by de Vos et al,[5] only 1 group used the validated Victorian Institute of Sports Assessment-Patella score.

Relying on high-quality human RCT studies with consistent findings results in less bias and provides the most objective, valid form of evidence for treatment effectiveness. Relying on a limited number of high-quality RCT intervention studies or low-quality RCT or non-randomized clinical trial studies with inconsistent or no findings to verify use results in the most bias and the least objective evidence. As of 2012, the authors of a few high-quality RCT studies consistently advocated autologous growth factor injections, leaving many unanswered questions that should be addressed in the future.

In conclusion, strong evidence indicates that autologous whole-blood injections for plantar fasciopathy are not superior to other treatments, and limited evidence suggests that PRP injections may be beneficial. Clinicians should be cautious about using these treatments and ask questions about how the injections were prepared and whether there is ample evidence for using the preparation for the condition and for the anatomical location being treated.

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