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Are Platelet Rich Plasma injections a Better Choice Compared to Glucocorticoid Injections for the Treatment of Rotator Cuff Tendinopathy in Adult Patients?

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Introduction

An estimated 16 to 34 percent of the general population will experience shoulder pain at some point in their life. Rotator cuff tendinopathy makes up a large portion of that percentage.[1] Platelet rich plasma (PRP) is an autologous blood product that has supraphsyiologic levels of growth factors and cytokines that have the potential to expedite the tendon healing process.[2] This literature review will look at the current science surrounding PRP and look at studies comparing its efficacy to the commonly used corticosteroid injection.

Background: Literature Review

Overview of rotator cuff tendinopathy:

Before the 1990s pain arising from a tendon was referred to as tendinitis. Referring to the injury as tendinitis implies that it has an inflammatory basis and this was widely accepted in the medical community. The treatment for this "tendinitis" was based on addressing the inflammation with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. However, with advancing histological techniques, new research by Puddu *et al* was emerging in the 1970s that there was an absence of inflammatory cells in chronic tendinitis.[3] Other studies showed collagen disruption, thinning and separation but with a lack of visible inflammatory process. With this new histological information available, the name was informally changed from tendinitis to tendinosis. This name change was supposed to aid in practitioners and patients understanding that this injury is not inflammatory but indeed degenerative. The tides may have changed again however. New studies in the early 2000s using immunohistochemistry and gene expression analysis showed the presence of an inflammatory infiltrate containing B and T

lymphocytes in tissue samples of Achilles tendon with chronic tendinosis.[4] The topic of inflammation in regards to injuries of the tendon, thus the term tendinopathy is used to cover all injuries arising from the tendon.[5]

Another debate exists surrounding rotator cuff tendinopathy; does it arise from pathology from inside the tendon (intrinsic) or from pathology surrounding the tendon (extrinsic)? Extrinsic pathologies include anatomical and biomechanical factors such as: subacromial spurs, acromion shape, acromio-clavicular spur, scapular kinematics, humeral kinematics, thoracic mobility and posture, pectoralis muscle length, scapular muscle performance, glenohumeral capsule performance and rotator cuff performance. The conceptual mechanism of the extrinsic pathology theory is compression of the tendon within the subacromial space from anatomical or biomechanical sources. Intrinsic pathologies include: tendon vascularity, tendon biology, tendon morphology, tendon mechanical properties, genetic predisposition, collagen content and morphology. The conceptual mechanism of the intrinsic pathology theory is degeneration of the tendon from tensile loading exceeding the intrinsic healing responses. It is most likely that both intrinsic and extrinsic causes are present in most cases of rotator cuff tendinopathy. Both of these processes of injury are potential targets for treatment. It is unclear at this time if modifying the treatment based off a patient's exact cause of tendinopathy is beneficial.[6]

Current Treatment:

The basic initial treatment for rotator cuff tendinopathy includes rest, ice and non-steroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs are controversial due to the debate that blocking the inflammatory process during the initial healing process may

actually delay healing. It is also unclear whether NSAIDs provide any relief if there is not an inflammatory process going on.[7] A review of 32 studies addressing the benefit of NSAIDs in tendinopathy found only nine well done, placebo-controlled trials. Of the nine studies, five showed some analgesic effect from NSAIDs; however, none looked at tendon healing.[8] There are several adjunct treatments that are hardly used which include: electric stimulation, phonophoersis, iontophoresis, laser and therapeutic ultrasound. There is little evidence to support the use of these adjunct treatment options. Physical therapy is a mainstay of treatment for rotator cuff tendinopathies. The extrinsic factors discussed earlier are very similar to the biomechanical abnormalities found in those with shoulder impingement syndrome, therefore the therapy is generally the same. A good rehabilitation program should include: range of motion exercises, stretching and strengthening of the rotator cuff muscles, balancing of muscular tone of the rotator cuff muscles, scapular stabilization and control as well as eccentric strength exercises of the rotator cuff. Eccentric strengthening is utilizing muscle contraction while the muscle is lengthening and has been shown to promote tendon healing and decrease pain in patients with chronic rotator cuff tendinopathy.[9] If there has been no pain relief in two to three months with conservative treatment then other treatment options including glucocorticoid injections and Topical glyceryl trinitrate. Glucocorticoid injections will be discussed in great detail in the next paragraph. Topical glyceryl trinitrate works by causing vasodilation and increasing blood flow to the tendon. It has been shown to decrease pain and increase strength after 24 weeks of continuous use in patients with chronic supraspinatus tendinopathy.[10] There are some experimental treatments that are emerging which include: topical NSAIDs, hyperthermia, extracorpeal shock wave therapy and

platelet rich plasma (PRP). PRP will be discussed in great detail in the upcoming paragraphs, as it is the treatment in question for his literature review.[11]

Corticosteroids in the treatment of rotator cuff tendinopathy:

Corticosteroid injections are commonly used to treat rotator cuff tendinopathy that does not respond to more conservative treatment options. Corticosteroid injections do have multiple side effects and questionable efficacy however. Side effects include: skin atrophy, fat necrosis, skin hypopigmentation, infection and possible systemic effects. There is also the potential side effect on tendon mechanical integrity as well. There have been several case reports of tendon rupture following the administration of corticosteroid injections, particularly the Achilles, biceps brachi and supraspinatus.[12]This evidence is based of intratendinous injections and there is not sufficient evidence to discuss peritendinous injections in regards to tendon mechanical integrity. A systematic review showed only a slight benefit of corticosteroid injection at four weeks and no benefit compared to NSAIDS.[13] Another systematic review by the American Academy of Orthopaedic Surgeons found there is little efficacy for subacromical corticosteroid injections in rotator cuff tendinopathy.[14] However, another review found that subacromial corticosteroid injections were beneficial up to nine months for rotator cuff tendionpathy and were superior to NSAIDs.[15] A 2016 meta-analysis found that after 3 months corticosteroid injections were no better than placebo for adults with rotator cuff tendinopathy. This meta-analysis also found that for every 5 patients treated, 1 would experience a slight, transient reduction in pain. They also found that pain did not improve with multiple injections.[16] A systematic review was done to see if corticosteroid injections were superior to anesthetic injections alone in the treatment of rotator cuff

tendinopathy. The review concluded that corticosteroid injections were more beneficial compared to anesthetic injections only up to 8 weeks. Mid-term and long-term outcomes showed no difference between the corticosteroid and anesthetic injection.[17] A systematic review of 50 studies (13 human, 36 animal, 1 animal/human) looked at the effects glucocorticoid injections had on tendons. In the review, 6 studies showed a loss of collagen organization and 3 studies found an increase in collagen necrosis. 8 studies also showed that the proliferation and viability of fibroblasts were reduced. The review found that in 17 studies there was a decrease in collagen synthesis. A meta-analysis from that review showed a significant reduction in mechanical properties of the tendon from the steroid.[18] A controlled laboratory study looking at supraspinatus tendon biopsies before and after treatment with either corticosteroid injection or surgical rotator cuff repair was done to look for any histological or immunohistochemistry differences. The first difference in the tendon tissues post treatment was an increase in nuclei and vascularity noted in the surgical group but not with the corticosteroid group. The ionotropic *N*-methyl-D-aspartate receptor 1 (NMDAR1) glutamate receptor was only increased in the corticosteroid group. This increase in the NMDAR1 receptor increases the suspicion for excitotoxic damage to the tendon following corticosteroid injections.[19]

Platelet Rich Plasma in the Treatment of Rotator Cuff Tendinopathy:

A prospective open label study that looked at the effectiveness of platelet rich plasma for the treatment of rotator cuff tendinopathy showed significant improvement in pain at 12 and 52 weeks. There were also significant improvements in functional strength tests, especially in external rotation. MRIs were also done before and at 4 and 8 weeks post

PRP treatment, 16 out of the 18 shoulders had improvements in their MRI severity scores. However, this study had no control to compare the PRP group against.[20] A different randomized controlled trial was done that compared PRP versus a saline placebo for chronic rotator cuff tendinopathy. All patients also were part of a 6-week standard exercise program. Outcome measures were the Western Ontario Rotator Cuff Index (WORC), Shoulder Pain and Disability Index (SPADI), 100-mm visual analog scale [VAS] of shoulder pain with the Neer test, and shoulder range of motion. These were assessed at baseline and at 3, 6, 12, and 24 weeks and 1-year post injection. The study showed no significant difference in any outcomes at any of the assessment points between the PRP group and the placebo group.[21] A multicenter retrospective review looking at the efficacy of platelet rich plasma for chronic tendinopathy resistant to conservative treatments showed the majority of patients reported a moderate improvement in pain. The retrospective review used patient data from four academic sport centers across the United States and had data from 180 men and women. The most common injection sites were the lateral epicondyle, Achilles, patellar tendons, rotator cuff and hamstrings. The outcomes were based off of VAS pain scores, assessment of functional pain and patient satisfaction. The results showed that 85% of patients were satisfied with their procedure and the average drop in VAS pain score was 75% (from 7.0- 1.8). This data came from a follow up survey that on average was completed 15 months after the procedure.[22] A 2017 meta-analysis looking at the efficacy of platelet rich plasma in the treatment of tendinopathies included 18 studies and 1066 participants. This meta-analysis was interested in determining what form of PRP was most effective and also accounted for the type and effectiveness of the control used. This meta-analysis

found the most significant outcomes from PRP groups were from leukocyte rich PRP (LR-PRP) compared to leukocyte poor PRP (LP-PRP). They also found that there was not a significant difference in control injections that included: saline, corticosteroids, local anesthetic and dry needling. They concluded that systematic reviews and meta-analysis involving PRP preparations should from now on account for the specific type or PRP used because it does make a difference.[23] A study out of The Journal of Bone & Joint Surgery aimed to test the effectiveness of PRP with different levels of leukocytes. They used three different compositions of PRP and were looking at levels of inflammatory cytokines as outcome predictors for tendon healing. One with reduced levels of leukocytes, one with standard levels of leukocytes and one with higher levels of leukocytes. The samples of PRP were used in vitro with horse flexor digitorum superficials tendon. The PRP with lower levels of leukocytes was found to have lower levels of interleukin-1B expression as well as lower levels of TNF- alpha expression. The authors of this study conclude that PRP with lower levels of leukocytes may be more optimal for healing due to lower levels of inflammatory cytokines.[24]

An in vitro study looking at levels of tenocytes proliferation and production of extra cellular matrix was done. Tenocytes from patients with chronic rotator cuff tendinopathy were cultured with either placebo or a medium with 10% platelet released growth factors. The tenocytes from chronic rotator cuff tendinopathies have been shown to be unable to synthesize the normal amount of fibrocartilaginous extracellular matrix that is needed for sufficient tissue quality. The study found that tenocytes treated with platelet released growth factor had higher levels of proliferation and extra cellular matrix production than placebo and it actually matched levels of healthy tenocytes.[25] PRP has the potential to

expedite the healing process by various growth factors and cytokines that are released by alpha granules in platelets when they become activated. The cytokines identified in platelets include transforming growth factor (TGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I, IGF-II), fibroblast growth factor (FGF), epider- mal growth factor, vascular endothelial growth factor (VEGF), and endothelial cell growth factor. These cytokines work by influencing cell proliferation, cell differentiation, chemotaxis and angiogenesis. There are also bioactive factors in the dense particles in platelets that include: serotonin, histamine, calcium, dopamine and adenosine. These factors also play an important role in wound healing. The platelets delivered in PRP are delivered in a clot. This clot in theory can also aid in healing as it may act as scaffolding in which other cells can bind on and begin the wound healing process.[2]

PRP versus Control Injections:

A study comparing the efficacy of PRP versus corticosteroid injections for symptom reduction in patients with partial rotator cuff tears was done. The study showed that the PRP after 12 weeks had significantly reduced VAS scores and functional pain scores. However, after 6 months there was no difference in efficacy between the PRP and the corticosteroid injection.[26] Another randomized control trial compared the efficacy of PRP versus corticosteroid injections for chronic rotator cuff tendinopathy. The results of that study showed that both groups improved in pain and shoulder range of motion and strength and there were no statistically significant differences between the two groups.[27] A study looking at the efficacy of PRP versus dry needling for the treatment of chronic rotator cuff tendinopathy was done. The PRP was shown to be more effective at 6 weeks and 6 months in reducing pain and disability compared to the dry needling. There were

not adverse effects in either group.[28] A study with 100 patients was done comparing the efficacy of PRP versus corticosteroid injections for the treatment of lateral epicondylitis. The patients treated with PRP were more often successfully treated, with the definition of being successfully treated a 25% reduction in VAS or Disabilities of the arm, shoulder and hand (DASH) score. Both groups baseline scores improved over 2 years, however, the DASH scores of the corticosteroid group only returned to baseline compared to the PRP groups scores, which significantly improved.[29]

Methods

I conducted a literature review of the scientific literature using Google Scholar as my web search engine. The search only included articles that used platelet rich plasma and/or corticosteroid as the primary intervention and no surgical studies were included. Articles were included that were not specific to the rotator cuff due to the vast amount of articles found on tendinopathy as a whole. The primary search was for articles from 2011 to the present, however, articles cited in the articles found in the original search were also used. The following terms were used in the search: “platelet rich plasma”, “PRP”, “Corticosteroid injection”, “glucocorticoid injection”, “rotator cuff tendinosis”, “rotator cuff tendinopathy”, “tendinopathy”, “tendinosis”, and “tendon”.

Discussion

Rotator cuff tendinopathies are one of the most common causes of shoulder pain that patients are seen for. There are numerous factors that can contribute to rotator cuff tendinopathies including both intrinsic and extrinsic factors. Intrinsic factors include lack of sufficient vascularity to the tendon as well as lack of proper healing. Extrinsic factors include anatomical and biomechanical abnormalities.[6] There is still debate in the medical

community on the amount of inflammation present in tendinopathy as well as even the use of NSAIDs for conservative management.[7] Other then the use of NSAIDs, the conservative management of rotator cuff tendinopathies is not really debated, the use of rest and ice are well-accepted first line options. Corticosteroid injections are commonly used to treat the pain associated with rotator cuff tendinopathies. However, the corticosteroids very questionable efficacy and a host of side effects associated with them. Corticosteroid injections have been shown to decrease collagen synthesis and reduce the mechanical properties of tendons.[18] There also have been several case reports of tendon rupture after corticosteroid injections.[12] There is also the potential for systemic side effects from corticosteroid injections. The efficacy of corticosteroid injections for rotator cuff tendinopathy is also questionable. A systematic review by the American Academy of Orthopaedic Surgeons found that there is very little efficacy for steroid injections in the treatment of rotator cuff tendinopathy.[26] Given all of the potential side effects and proven low efficacy of corticosteroid injections, patients and providers are looking for better options. With the proven in vitro studies confirming PRPs efficacy to promote healing it would seem as if PRP would be a superior option to corticosteroids for rotator cuff tendinopathy.[2] PRP has been used as an adjunct to expedite healing and reduce blood loss for some time now. Its use to expedite healing in soft tissue injuries is fairly new and has very limited research. It has been proven to work superior to corticosteroids in the treatment of lateral epicondylitis.[29] However, the current studies do not prove that efficacy translates to the rotator cuff. Direct comparison studies of PRP versus corticosteroid injections in the treatment of rotator cuff tendinopathy are conflicting. Some show some benefit of PRP over corticosteroids and others show no difference.[26-27]

A large meta-analysis looking at the efficacy of PRP in the treatment of tendiopathies in general found PRP to be generally more effective than other injectable controls. This review also found that PRP with higher levels of leukocytes were more effective then PRP with lower levels of leukocytes. Another study found the exact opposite and came to the conclusion that PRP with reduced amounts of leukocytes were more effective for healing.[23-24] PRP is still very new and has been proven to work in vitro and in other forms of tendinopathy. The research is just lacking when it comes to its efficacy in the treatment of rotator cuff tendinopathies. With the different types of PRP and injections techniques; higher quality studies are needed that control for the PRP specifics. I do believe PRP and other orthobiologics will have a place in management of tendinopathies in the future. I also believe that amount of corticosteroid injections will decrease in the treatment of tendinopathies based off of the known tendon damage and rupture risks present. As a future practicing physician assistant (PA) I plan on keeping a keen eye on new research surrounding PRP for the treatment of various tendinopathies. With the knowledge from this literature review I will be able to better educate my patients on the risks and benefits of corticosteroid injections for tendinopathies. In the eyes of a good amount of the general population corticosteroids are like a miracle injection, but the reality is the current data does not back that up. As a PA I will look out for my patient's best interest, whether that be with old but reliable treatments or with new cutting edge treatments. I believe orthobiologics are just at their beginning and I look forward to following the up and coming research.

Conclusion

Platelet rich plasma has use as a minimally invasive treatment for several orthopedic conditions; however, the current research for its use in rotator cuff tendinopathies is just not strong enough yet. The current literature out currently is just not clear if it works or how well it does work. The studies comparing PRP versus corticosteroid injections in the treatment of rotator cuff tendinopathies are conflicting.[26-27] Both of these studies do show that PRP is either just as good or better than corticosteroid injections in the treatment of rotator cuff tendinopathies. With the proven poor efficacy of corticosteroid injections and the potential risks involved, PRP seems to be a safe option with results that are either better or comparable to steroids. More studies are needed to look at efficacy, long term efficacy, PRP formulation and injection protocol.

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