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**Knee Osteoarthritis: Efficacy of Platelet-Rich Plasma Injections Are Non-Inferior to
Conventional Joint Injection Treatments**

By

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INTRODUCTION

Osteoarthritis (OA) continues to affect the quality of life for over 30 million Americans.¹ This disease process can affect many different joints in the body, limiting motion and participation in occupational or social events and potentially causing debilitating pain. The only definitive treatment for OA, seemingly, is to surgically replace the affected joint(s). There are many in the medical field who have sought an alternative treatment to either slow the disease progression or mitigate symptoms from OA, which is preferable when compared to total arthroplasty.

Early in the disease process, OA can cause unpleasant symptoms and begin to affect patients' lives, limiting their work and preventing them from participating in various activities of daily living (ADLs). People often turn to over the counter (OTC) medications, like Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) to control the pain they experience, which can have unfavorable effects on the body from chronic use. There is a desire for less-damaging alternatives to alleviate pain and improve function for patients living with OA. The standard approach to treating OA is to reduce overall weight, avoid aggravating movements, apply ice, administer NSAIDs and utilize an appropriate physical therapy treatment plan.¹ These conservative methods should be exhausted before exploring other options, such as opioid prescriptions, pain management referrals and, finally, a referral for total joint replacement.

Knees are among the most common joints affected by OA. These joints undergo an exponential load with even the most common tasks of ADLs, like descending stairs. Knees absorb a large amount of force and distribute this during movements of landing harshly, lunging to grab something, jogging, and lifting various objects. People in America are not typically

trained at an early age to properly navigate these movements for the sake of their knees and back, leading to improper distribution of force and ultimately leading to the progression of OA.

There are many factors that contribute to the onset of OA in individuals that are sometimes either preventable or would ultimately delay the degradation of the articular cartilage and narrowing of joint space. The “Q Angle” can change, affecting a patient’s kinematic chain, putting the impact of the knee joint into an unfavorable position for optimal distribution of force on the articular cartilage. This negative change in Q Angle typically affects the joints above and below the knee, which will ultimately lead to a subsequent onset of joint pain or ultimately degenerate into OA. One’s occupation can greatly contribute to the overuse of the knee joints, increasing daily demand over many years and degrading the articular cartilage along with narrowing the joint space. Genetics may play an important role in contributing to the declination of knee articular cartilage, independent of chronic overuse.

The mechanism of OA degradation stems from mechanical loading and increased presence of proinflammatory cytokines: IL-1, TNF Alpha, nitric oxide, matrix metalloproteinases, aggrecanases, and prostaglandins.² Other factors contributing to knee joint OA are the absence or limited presence of growth factors (GF), collagens, proteoglycans, and anti-inflammatory cytokines (IL-4, IL-10).² NSAIDs would primarily work by eliminating only one harmful subset of cytokines, prostaglandins. This, along with other conservative treatments, limits the effectiveness and longevity of relief from pain and improvement of function.

Platelet-Rich Plasma (PRP) aims to mitigate symptoms and restore functionality to the knee joint(s) by decreasing the presence of proinflammatory cytokines and increasing the proliferation and genesis of the anti-inflammatory, growth promoting factors listed above. Platelets contain these anti-inflammatory cytokines and growth factors, which will allow for

stimulation of cellular growth, angiogenesis, regeneration of tissue and synthesis of new collagen.² By concentrating the amount of injectable platelets, this maximizes the potential for optimal relief of symptomatic OA and, ideally, the regeneration of the dissipated cartilage.

Health care providers strive to avoid referring patients with knee OA to surgery due to the inherent risks, the arduous task of regaining acceptable functionality, potential loss of their range-of-motion (ROM), unforeseen sequelae, potentially unfavorable fragility of the patient, and the limited lifespan of the traditional knee arthroplasty. Artificial knee joint replacements typically last approximately ten years, which may also be shortened with patients who are more active than their counterparts. The need to manage symptoms and slow the progression of OA with alternative means is in great demand, especially treatments which have high efficacy for longer durations.

One of those alternatives is injecting corticosteroids (CS) within the affected knee joint(s) to decrease the inflammation and ultimately decrease the swelling and pain. This approach is common in medical practices but has its pitfalls. CS can relieve pain and provide people greater function and ROM temporarily, but this will not typically last more than several weeks to months, which requires patients to return often in order to regain this level of relief. The standard interval of CS injections ranges from every three to six months, which comes at great cost to the patient if they have substantial co-pays or exceed the allotted amount of coverage by their respective health care insurance. Chronic use of CS injections will have adverse effects, primarily on tissue degradation and heightened blood glucose levels caused by chronic use.³

Hyaluronic Acid (HA) is another accepted treatment for knee OA, creating synthetic cross-fiber links in the articular cartilage and subtly strengthening the hyaline cartilage in the knee joint.⁴ There does not appear to be common adverse effects from the continued use of HA,

but it does require intra-articular injections to be administered frequently. The lack of efficacy from HA treatments dissuaded the medical community from establishing these injections as the gold standard of care.⁴

Platelet-Rich Plasma (PRP) has emerged as a promising treatment of OA, particularly in large joints. For the treatment of knee OA PRP is non-inferior to the traditional methods, in improving function, pain, and ADLs. PRP is promising due to its autologous nature and appeal with the ever-increasing push for holistic or “natural” options in therapeutics. The patient will utilize properties of their own body to bolster an anti-inflammatory response and potentially improve the function of the knee cartilage.³ Although it requires fluid collection from a patient and processing which may be slightly time intensive, it offers an alternative to synthetic and potentially harmful traditional interventions in CS and HA injections.

EFFECTIVENESS OF PRP

To utilize PRP, the evidence must demonstrate that the treatment is a non-inferior choice, compared to HA and CS. The measure of effectiveness is primarily based on scores that are either subjective, or an attempt to convert subjective symptoms (i.e. pain) into objective values. These scoring systems quantify questionnaires or standardized written measurements into data points, allowing researchers to provide adequate analysis of each therapy’s efficacy. Although there are many different concentrations, injection intervals, variable injection sites and length of time studied, the overall effectiveness will be outlined in this section and the variables of application will be addressed in the discussion.

In a study by Duymus et al., researchers examined the efficacy of treatment between PRP, HA and Ozone gas. The researchers observed an initial improvement of symptoms in the first month from Ozone gas, PRP and HA. The Ozone gas therapy did not significantly alleviate

pain or improve function past the first month. HA and PRP did not have any significant statistical differences at any of the evaluations within the first six-month period. However, the PRP group improved across both Visual Analog Scale (VAS) and Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) scores, compared to the HA treatment cohort. The VAS score is a subjective measurement for a patient's pain rating. WOMAC is a tool used to assess pain, stiffness and functionality in patients with OA. These results led the authors to believe that PRP is a superior treatment option for mild-moderate knee OA, when compared to HA and Ozone gas therapies.⁵

Unlike the Duymus study, an Italian study found that PRP and HA only improved knee OA symptoms slightly.⁶ This study was submitted and accepted by the American Journal of Sports Medicine in 2015, and provided evidence that PRP IAI's Intra-Articular Injections (IAI) did not show superiority when compared to viscosupplementation.⁶ Filardo and colleagues utilized a plethora of measurement tools to directly compare each therapy. The double-blinded randomized-control trial showed evidence that both PRP and HA slightly improved effectiveness in improving knee functional status and decreased the severity of all patients' symptoms. However, the researchers did not feel either treatment yielded a significant clinical or statistical improvement to recommend either for therapeutic use.⁶

Subjective measurements alone are, seemingly, tools that can only provide limited data for PRP treatment. In a 2016 study out of Rush University Medical Center, researchers measured the effectiveness of PRP and HA via biochemical marker concentrations as an additional measurement to standardized subjective scoring systems. PRP application demonstrated improved scores throughout the duration of the study, for the subjective questionnaires. However, there was a considerable decrease in synovial proinflammatory cytokines after one

year of PRP treatments. The researchers argued the reduction in concentration of these cytokines, from PRP therapy, likely contributed to the improvement of function and relief of pain symptoms in these patients.⁷

PRP demonstrated not only non-inferiority to conventional viscosupplementation, but also superiority to HA in the Duymus and Cole studies. These findings suggest that PRP treatment is a viable means to managing knee OA pathologies. However, the Filardo researchers observed minimal improvement and did not recommend either PRP or HA for management of knee OA. The data from this research demonstrates PRP's effectiveness compared to conventional therapy.

PRP EFFECTIVENESS ON DIFFERENT GRADES OF OA

It is generally accepted that treating knee OA earlier on and with a younger patient tends to have better outcome potential. How far along someone is in the disease process can have implications for their prognosis and influence management. The Kellgren-Lawrence system for classification of osteoarthritis of the knee, commonly used in OA research, is graded from doubtful (1) to severe (4). Jubert et al performed a study on geriatric patients with severe knee OA (Grade 4), comparing PRP to CS injection therapies. This team discovered there was not any significant difference in the effectiveness of both treatments after six months.⁸ Although not statistically significant, this provides mounting evidence for the non-inferiority of PRP utilization when compared to CS therapy.⁸ Gormeli and colleagues suggest that treating patients with Grade 4 OA is not beneficial and does not improve symptoms or composition of cartilaginous tissue.³

EFFECTIVENESS OF PRP ON DIFFERENT AGE GROUPS

As people age, there tends to be a global diminished response to injury and ultimately healing. The effects of knee OA over time will continue to deteriorate the already affected

articular cartilage and subsequently impair the function of knee joints. This can lead to increased pain and decreased functionality. As fragility scores increase, surgeons are apt to deny patients knee osteoplasty. Treatment should focus on alleviating symptoms and initiating a therapy that will limit tissue degradation. In geriatric patients, PRP treatment was shown to be non-inferior to CS injections. PRP produced no adverse effects when given as a single injection with a duration of effect of up to six months after a single dose was administered.⁸ If PRP can eventually become covered under plans like Medicare this would provide a much-needed therapy without the harmful tissue degradation, often seen in chronic CS injections.

POTENTIAL VARIATION IN INJECTION SITES

Providers need to identify the proper injection site(s) for PRP treatment. Traditionally IAI is done for all treatments, when treating knee OA. There is potential for better outcomes by combining IAI with Intraosseous Injections (IOI), in the medial tibial plateau and the medial portion of the femoral epicondyle, thus penetrating deeper layers of the cartilage and asserting better therapeutic outcomes. One study found that combining IAI with IOI provided better overall and total WOMAC scores and increased duration of effect.⁴ If feasible, this may become a new standard in place of PRP, or the combination of PRP with HA, to decrease pain and increase functionality.

EFFECTIVENESS OF COMBINING HA AND PRP INJECTIONS

To date, the standard approach of managing the symptoms of knee OA is utilization of a monotherapy: either HA or CS, when indicated. Lana and colleagues randomly selected three groups which tested the effects of PRP IAI alone, HA IAI alone and the combination of PRP and HA IAI's. Each group received three IAI's of their respective assigned treatment, with two-week intervals between each injection. The subjects returned for evaluation at months 1, 3, 6, and 12.

They utilized the WOMAC and VAS scores to quantify the efficacy of each of the therapeutic agent(s). The PRP group had significantly better outcomes, compared to HA alone, throughout all follow-up evaluations in this study. The combination group yielded vastly greater results with increased physical function and reduction in pain during months 1 and 3. The Lana study suggested that combining the two treatments will provide better outcomes in the first 30 days after onset of treatment and continuing treatment with PRP alone will improve quality of life, in comparison to HA alone.⁹

DISCUSSION

PRP is a desirable intervention, that may allow health care providers greater options in managing patients with knee OA. The ability of a patient to exercise their own judgement to select an appropriate therapy for their OA is invaluable to providing the best care. Further substantial research and raised awareness for this intervention may lead to insurance providers including PRP within their coverage and granting patients a viable and effective means of managing their knee OA. Smith and colleagues completed an FDA-sanctioned, randomized control, double-blinded, placebo-controlled study in 2016, attempting to provide results that would prove the safety and efficacy of utilizing PRP as a monotherapy in treating knee OA.¹⁰ Their results yielded no adverse events and displayed statistically significant improvement in the PRP group over the twelve-month study.¹⁰ With FDA-sanctioned studies, like this one, it gives promise that PRP may become a more available adjunct treatment for knee OA in the near future and give providers the option of recommending its use to their patients.

The limitations of all research studies examined were identified clearly. There are no guidelines in any of the studies that suggested a definitive composition to the PRP solution for

their injections. This may have skewed the results of their research, either providing too much PRP or too small a quantity. There needs to be an established proportion of PRP which, in turn, will allow health care providers the ability to begin with an effective dosing and tailor the solution with everyone treated. Dosing may also need to be scaled in accordance with the BMI of a patient or a patient's age. Secondly, there was not an agreed upon or established interval for the injections, which may have degraded the efficacy of PRP in these studies. Thirdly, there was variation amongst the studies in regard to either additions to the PRP injectable solution or modifying the PRP solution prior to administration (i.e. Photo-activated PRP).¹¹ Also, the injection site(s) have not been clearly established, with one study injecting PRP into the joint-space of the knee and within the sub-chondrolar bone.⁴ The additional injection sites may prove to decrease inflammation not only within the knee joint, but also in the peri-articular tissue, which may increase its efficacy. Finally, there is an absence of multi-year studies, which may provide better insight into the sustained benefits of utilizing PRP for knee OA treatment.

The strength of these studies lies within the randomized control trial approach. The evidence provided was reliable and allowed the results to be trusted. Also, the consistency of comparison to other means of management allowed for analysis between traditional interventions and the various PRP treatments.

There is a strong desire by researchers to provide further research for PRP injections in the treatment of knee OA. A large scale, longevity study will provide adequate data to inspire health care providers and biomedical researchers to consider PRP as a non-inferior method of treating chronic OA. Without proper funding and standardization to dosing there will ultimately be pitfalls for approving PRP as an acceptable alternative to traditional methods of care for knee OA.

CONCLUSION

PRP has a great amount of potential to aid in the control of symptoms and potentially regrow degenerated cartilage in patients suffering from knee OA. Overall, the research reviewed provided adequate evidence to consider PRP non-inferior to HA or CS. Adding PRP to a provider's treatment options greatly benefits patient care for those affected by knee OA in K-G grades 1-3.

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