4-1-2019

Comparing Intra-Articular Injections of Hyaluronic Acid versus Platelet Rich Plasma for Osteoarthritis Knee Pain

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By

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Capstone Project

Submitted to the Faculty of the

Department of Physician Assistant Education

of University of the Pacific

in partial fulfillment of the requirements

for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

April 2019

ABSTRACT

Purpose: To compare the efficacy of intra-articular (IA) injections of hyaluronic acid (HA) viscosupplementation to platelet-rich plasma (PRP) for degenerative osteoarthritis (OA) knee pain and function

Methods: A review of current high-level evidence research articles on the subject matter

Results: PRP is more effective than HA injections for mild knee OA, but there are no significant differences between PRP and HA in effectiveness for more advanced knee OA. Combination therapy of HA and PRP is superior to PRP or HA alone. Multiple PRP injections also improve pain and function in comparison to multiple HA injections or single PRP injections.

Conclusion: The existing clinical studies show promising data that PRP is a more effective treatment for early knee OA in comparison to HA, but further studies need to be performed for more conclusive results.

Key Words: hyaluronic acid, platelet-rich plasma, intra-articular injection, knee, osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a gradually progressive degenerative joint disease due to the loss and destruction of cartilage from an inflammatory process, most commonly affecting the elderly. OA results in pain, decreased joint range of motion, and significantly affect activities of daily living and quality of life when severe.[1] Two hundred and fifty million people worldwide suffer from knee OA, of which 27 million are Americans.[2] This number is expected to increase with the continued growth in the geriatric population due to the baby boomers.

In view of the morbidity from OA, the goals of treatment often include pain relief, reducing inflammatory signs, and restoring function. Current clinical practice uses various conservative treatment options to achieve these goals prior to resorting to total knee arthroplasty.

The Osteoarthritis Research Society International (OARSI) most recent guideline for non-surgical management of knee osteoarthritis recommends first-line treatment as physical therapy, including land and water-based exercises, weight management, strength training, and biomechanical interventions.[3] Physical therapy is often used in combination with medications, such as oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. However, oral acetaminophen and topical NSAIDs are less effective than oral NSAIDs. Unfortunately, many patients cannot tolerate the long-term systemic adverse effects of full-dose oral NSAIDs, as doing so may increase the risk for gastrointestinal bleeding or kidney failure. Because of these possible complications, oral NSAIDs are contraindicated in patients with certain pre-existing conditions such as chronic kidney disease or peptic ulcers.[4]

When physical therapy and oral drug therapy fails, standard treatment resorts to a trial of injection therapy. Intra-articular (IA) injection therapy has become more popular over the past few decades. Corticosteroids are frequently used as the first line and most cost-effective option by targeting the inflammatory process of knee OA.[4,5] The OARSI recommends IA corticosteroid injections, while the American Academy of Orthopaedic Surgeons (AAOS) still finds this treatment inconclusive.[3,6] Many side effects are associated with corticosteroid injections, such as post-injection flare, flushing, facial swelling, skin depigmentation, subcutaneous atrophy, articular cartilage changes, increased blood glucose levels in diabetics, osteoporosis, and tendon atrophy.[5]

Because of the strong side effect profile of IA corticosteroids and the limited number of injections a patient can receive in a given time period, researchers have moved onto synthetic hyaluronic acid (HA) injections for patients with symptomatic knee OA. HA is endogenously produced by the human body, but its levels are decreased in the synovial fluid of OA joints. The

principal behind injecting HA into the joint space is to bring the viscoelasticity of the synovial fluid back to baseline in an effort to further prevent further degeneration of articular cartilage.[5] Many different brands of HA with varying molecular weights are sold throughout the world, but overall, HA is an extremely costly therapy ranging from $750 to $1368.[5] In addition, the AAOS exercises a strong recommendation against using hyaluronic acid (HA) injections for patients with symptomatic knee OA.[6]

Platelet-rich plasma (PRP) is another injection therapy that was first introduced in the 1950s. The application towards OA treatment is still new, with many recent studies attempting to explore its efficacy. The appeal of PRP is the ability to use an autologous blood product, rich in growth factors and cytokines, that produces anti-inflammatory effects for tissue healing and stimulates cartilage regeneration.[2] The current AAOS position on PRP injections as a treatment for symptomatic knee OA is that the evidence is inconclusive.[6]

The question remains, as to which injection therapy is most effective. The purpose of this paper is to determine whether current evidence supports the efficacy and superiority of IA PRP injections over IA HA injections for improving knee OA pain and function.

DISCUSSION

Mechanisms of Action

The biochemical and biomechanical mechanisms initiated by HA and PRP must be understood in order to effectively evaluate the efficacy of HA versus PRP for improving knee pain and function. Although both HA and PRP decrease the catabolism of cartilage in OA by suppressing inflammatory mediator concentrations, a controlled laboratory study found that PRP had a significantly greater reduction of specific protein-coding genes and increased expression of other genes to increase cartilage synthetic activity. This study harvested synovium and cartilage

from twenty-one patients undergoing total knee arthroplasty and exogenously co-cultured the samples in either PRP or HA media.[7] The limitation of this study is the small sample size in only a population with end-stage, severe OA, resulting in the restricted amount of assays due to the minimal amount of knee cartilage available for samples.

Another controlled laboratory study created cartilage defects in the femoral condyles of thirty rabbits and divided them into a PRP, HA, and control group. Histology, growth factors, cytokines, and platelet numbers were measured at six and twelve weeks. The PRP group exhibited better restoration of cartilage and subchondral bone compared to HA and placebo.[8] The strengths of this study include its significant results and being able to analyze histological samples of the cartilage. However, the limitations include the small animal sample size and the short duration of the study.

In a controlled laboratory study where cells from articular cartilage and synovium of the knee were isolated from twelve patients undergoing anterior cruciate ligament reconstruction and combined with PRP culture media and control groups. Results showed that PRP significantly stimulated both cell proliferation and secretion of superficial zone protein, which lubricates articular cartilage, over the control group. These changes decrease the amount of friction and bone on bone pain of knee OA.[9] Although this study highlights PRP effects on more mild forms of OA in humans, the limitation includes small sample size without a comparison to HA.

A double-blind, randomized clinical trial conducted from a sample size of 336 patients with knee OA showed that PRP in comparison to placebo was able to reduce the amount of inflammatory and pro-angiogenic factors, thus decreasing both joint inflammation and synovial degeneration in patients with knee OA. PRP also promoted neovascularization and decreased the damaged cartilage areas in these patients. This study also focused on the pharmacokinetic

analysis of PRP and found its most optimal dosage to be 10 milliliters and peak concentration at 12 hours post-treatment, which is relatively quick compared to other forms of injection therapy.[10] Although this study does not compare PRP to HA, it was able to incorporate a satisfactory sample size with a placebo group in a human trial and use MRI analysis to further support the positive effects of PRP.

Knee Pain and Function Efficacy

As much as HA and PRP can modify growth factors, cytokines, histology of synovial fluid and knee joint analysis via MRI or CT, the efficacy of these treatments is better measured through patient improvements in knee pain, function, and overall quality of life. Commonly accepted tools for measuring these changes are the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, stiffness, and physical function scales, Visual Analog Scale (VAS) for pain, Knee Society's Knee Scoring System (KSS), Knee and Osteoarthritis Outcome System (KOOS), International Knee Documentation Committee (IKDC) subjective knee evaluation, and the Lysholm knee score.

The WOMAC, VAS, and IKDC scales were used to measure the efficacy between PRP and HA in a level I, prospective, randomized, double-blind, comparative clinical trial in 111 patients with mild to moderate knee OA. PRP was statistically and clinically more effective than HA.[11] Similarly, a level II, prospective, comparative study with 150 patients not only showed improvement of symptoms and function of knee OA in the PRP group compared the HA group, but also showed evidence of the longer efficacy with PRP injections.[12]

A retrospective study that focused on 118 patients with early knee OA comparing pre-treatment KSS and VAS scores with post-treatment scores at three and six months, showed that PRP was statistically more efficacious than HA.[1] In another prospective, randomized study of

120 patients with mild to moderate knee OA, followed at baseline, one month, three months, six months, and twelve months with WOMAC and VAS scales, PRP compared to HA was found to be superior. In addition, the PRP patients experienced at least 12 months of pain reduction.[13]

Although most studies indicated that PRP was more effective than HA, a few studies did not confirm that PRP was clinically superior to HA for improving pain and function scores. Evidence for the superiority of PRP over HA for middle-aged patients with moderate to severe knee OA is inconclusive.[14,15]

PRP + HA Combination Treatment

Given that PRP and HA target different factors biochemically and that the evidence is inconclusive for PRP superiority to HA in all levels of knee OA, researchers have considered whether combination treatment with PRP and HA might provide a more effective treatment for knee OA. A small, novel, laboratory study that created an in vivo arthritic cell by sampling human chondrocytes and combining the sample in either, a control, HA, PRP, and HA and PRP medium focused on the cellular-level benefits of the combination IA injections with HA and PRP. The synergistic effects of HA and PRP yielded increased stimulation of cartilage regeneration through chondrogenic signaling recovery to rescue cartilage from breakdown and decreased the number of inflammatory cells from pro-inflammatory cytokine-induced degeneration when compared to the other groups.[16] Similarly, another small study showed that HA increased the release of important growth factors from PRP.[17] However, both studies only sampled a small population and analyzed a limited amount of growth factors over a matter of days, rather than months.

Combination PRP and HA treatment is further supported in a double-blind, randomized, controlled prospective study of 120 patients divided into groups comparing the combination

treatment of HA and PRP to HA or PRP alone via the WOMAC and VAS questionnaires completed by participants at baseline and after treatment at 30, 90, 180, and 360 days. The combination group showed significantly less pain and improved functional outcomes in the first thirty days of treatment and improvements persisted from three months to a year.[18]

Multiple PRP Injections

The optimal number and frequency of PRP injections that are safe and effective are not well established. In clinical practice, IA corticosteroid injections are usually given no more frequently than every three months, although pain relief is patient dependent and may last only one to two months. IA HA injections are usually performed no more than every six months and tend to provide relief for a minimum of a few months.

In a double-blind, randomized, placebo-controlled trial of 182 participants with early knee OA, multiple PRP injections led to much better clinical results in comparison to one PRP injection, multiple HA injections, or multiple saline injections. However, remarkably no significant differences among the four groups were noted for patients with advanced knee OA.[19] On the other hand, a prospective, randomized study found that annual repetition of IA PRP injections further improved pain and function, which outcomes were somewhat comparable to the sustained pain relief with HA injections every six months.[20]

Summary of the Findings

Although the existing evidence shows that both HA and PRP play a role in improving inflammation and growth factors in knee OA, relieving pain, and improving function, studies are supporting the use of PRP over HA in the younger population and in those with mild knee OA. However, PRP is not more effective than HA in more advanced knee OA. The strengths of these studies include the strong level of evidence, good sample size, and variability in age and severity

of OA in the sample populations. The limitations of these studies include the lack of a control group in the prospective and retrospective studies based on ethical reasons and the absence of a comparison group with IA corticosteroid injections. Moreover, self-reported questionnaires measuring pain and function are subjective. Yet, obtaining radiographic images for follow-up to provide a more objective analysis are not commonly a part of these studies due to high financial costs. There were also a number amount of patients from the larger studies that were lost to follow-up. Most studies also had a short follow-up period and focused on monitoring treatment efficacy for only the first six months to one year following treatment. No long-term studies are currently available.

Evidence from these studies also showed that multiple IA PRP injections performed better than either multiple IA HA injections or single PRP injections. In addition, combination therapy of HA and PRP seemed to have a synergistic effect resulting in a greater improvement in the biochemical properties of knee OA, as well as providing symptomatic relief. Although these specific studies are promising, they are few in number. More research is needed to explore PRP injections and to determine a proper injection algorithm.

CONCLUSION

PRP does have a role in knee OA treatment, especially in younger patients with mild OA and in combination therapy with HA, but more research is needed to confirm these conclusions. With the pharmaceutical industry's release of new HA drugs and an extended-release IA corticosteroid that has less adverse effects, additional and more comprehensive research comparing all IA injection therapies will be necessary. Another factor important in drug selection is cost. Although HA injections are more expensive than PRP injections, most insurances currently cover HA injections with prior authorization from a clinician, whereas, PRP is mostly

cash-pay and not part of the insurance formularies. Moreover, not every clinical practice may have the means to afford PRP training of clinicians and the purchase of necessary supplies. Another important consideration is whether primary care physicians, as well as sports medicine physicians and orthopedic surgeons, can also offer PRP for OA treatment. However, these considerations will not be addressed until further research is conducted to establish the efficacy of PRP in standard clinical practice guidelines.

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