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Platelet-rich plasma intra-articular injections in reducing pain and improving function in patients with osteoarthritis

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Introduction

Osteoarthritis (OA) is one of the most common complaints encountered in the primary care setting today, and predominantly affects older patients. The increase in our aging population results in an increased frequency of OA overall, and hence, heightened demands on the healthcare system. To better understand osteoarthritis and how it impacts healthcare, it is important to understand the pathophysiology behind the disease. OA is a progressive disease that slowly destroys every structure in a joint including bone, and soft tissues, such as articular cartilage, joint capsule, and ligaments.[1] Furthermore, it is a chronic disease that can cause patients a considerable amount of pain and disability. Over time, OA causes the loss of articular cartilage in most joints, causing joint pain as the bones in the joint move across one another.[1] Without the protection of the articular cartilage, chronic inflammation begins to develop around the bone causing further destruction of the joint, resulting in pain and limiting mobility. This destruction of the joint causes osteophyte formation, which narrows the joint space and eventually limits the joint's range of motion. As the joint becomes increasingly calcified and the cartilage is further destroyed, the patient experiences increased pain and a reduced quality of life (QOL).[1]

Many treatment options are available to these patients; however, most are inadequate for long-term effectiveness and safety. Available therapies include physical therapy, OTC medications such as acetaminophen and NSAIDs, steroid injections, hyaluronic injections, and partial or total joint replacement surgeries.[2] Conventionally, OA is treated with analgesics, anti-inflammatory medications, physical therapy, and corticosteroid or hyaluronic acid injections in the affected joint. Although both types of injections are feasible options, in practice not all patients see improvement from steroids or hyaluronic acid.[2] Because of the low efficacy of

conventional injections and the recent push from patients for more natural treatment alternatives, new technologies have been developed over the past decade to alleviate pain and improve function in patients. Platelet-rich plasma, or PRP, is a relatively recent and promising new therapy for OA that is more natural and possibly more effective than conventional OA therapy. The proposed mechanism for PRP is that the growth factors and healing enzymes in a patient's blood (when isolated, concentrated, and injected into the affected or damaged joint) decrease joint inflammation, thus reducing pain and improving QOL. PRP therapy first starts with drawing blood from the patient. Next, the patient's blood is spun down and separated with a centrifuge. The blood separates with the red blood cells near the bottom and white blood cells and platelets near the top. The platelets accumulating in this layer contain many different growth factors that can be collected and injected into the patient's joint at a much higher concentration. PRP usually contains over 20 different types of enzymes, proteins, peptides and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor (TGF-beta), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) platelet factor 4, interleukin-1, and platelet derived angiogenesis factor.[3] In brief, the PRP injections contain enzymes and factors that promote healing, reduce inflammation, and promote regeneration of cartilage in joints.[3] These growth factors act on chondrocytes to help promote synthesis of the cartilage matrix, increase cell turnover, cell growth, cell migration, as well as promote protein transcription.[3] The premise of PRP's benefit is that its growth factors will set off a cascade of natural healing and regeneration of tissue in the damaged joint.

Not all PRP is made equally. Preparation methods and combinations of PRP vary widely in practice because a standard protocol has not yet been established. PRP also varies due to the different systems used to procure this solution. PRP is obtained by either a one-spin or a two-

spin process.[3] Systems that use a one-spin process separate the blood sample into two layers: RBCs with WBCs, and platelets. The platelet concentrations from the one-spin systems are usually 1-3 times greater than in whole blood and take less time to concentrate. This shorter preparation time removes the need for adding an anticoagulant to the blood in order to prevent clotting from occurring during the blood removal procedure and when the PRP is injected into the desired joint. Two-spin systems separate the blood into three distinct layers: RBCs, a buffy coat layer with platelets and WBCs, and a platelet depleted plasma layer. The layer desired in a the two-spin system is the buffy coat layer which typically contains five times the concentration of platelets than a one-spin system. Preparation times, however, are at least 30 minutes or more, which means these samples require an anticoagulant to prevent clotting during the process.[3]

Patients rarely have any adverse side effects from these injections. Because patients are receiving their own blood, the risk of any immunologic reaction occurring, if existent, is minimized. Nonetheless, as with any other injections, the risks of injection site reaction, infections and bleeding are still present. To prevent these potential complications from happening, PRP injections should be administered using aseptic technique.

Whether the complex and time-intensive requirements for administering PRP warrants its use for intra-articular (IA) therapy in OA is in question and should be examined. If PRP is at least or even more effective than corticosteroids or hyaluronic acid (HA) for relieving pain and restoring function, then it can be recommended with confidence to OA patients who are appropriate candidates for intra-articular injections. In addition, if its beneficial effects are more durable than other IA agents, it may become the preferred treatment of choice.

Discussion

Overwhelming preliminary evidence supports IA PRP injection as a possible option for treating OA in order to reduce pain and improve function. In a study by Guvendi et al, 57 patients with knee OA were randomized into three IA groups; group one received one corticosteroid injection, group two received one PRP injection, and group three received three PRP injections four weeks apart.[4] All groups were followed at two-month and six-month marks after the injection. Seven patients were lost to follow up; two in the corticosteroid group and five in the three-PRP injection group. A visual numeric scale and the Western Ontario and McMaster Universities Arthritis Osteoarthritis Index (WOMAC) were used to evaluate pain, stiffness, and function, while the Lequensne scale was used to assess physical function. For all injections, visual numeric scores showed a significant reduction in pain at rest, at night, and with movement. The 3-PRP injection group, however, showed the greatest improvement at the two-month mark. At the six-month follow-up, pain scores still reflected improvements compared with baseline evaluations. WOMAC scores also declined in the three groups but both PRP injection groups showed greater improvement than corticosteroids. The difference in WOMAC scores between three-PRP and one-PRP groups at the six-month follow-up, however, was not statistically significant. Nonetheless, PRP injections were found to be effective for at least six months in the patients who participated for the full length of the study. This evidence highlights that compared with steroid injections, PRP injections for Knee OA had more durable (longer-lasting) effects on pain and QOL. The study had no reports of edema or pain after any of the injections; however, they did have one participant in the single PRP injection group that experienced mild erythema which eventually resolved after six hours of cold therapy.[4] For these reasons, Guvendi et al. proposed that PRP IA injection is a viable and safe alternative to

corticosteroids for OA of the knee.[4] While the study showed great significance in better WOMAC and Lequensne scores by using PRP injections, it was limited by a small sample size, and brief follow up time. The researchers also state that due to the lack of a placebo and a control group, the participants were not blinded in this study. The study also suggested that accuracy in injection placement could be improved by using ultrasound guidance techniques.[4]

Glynn et al. researched the feasibility of relieving OA pain with PRP injections as well as whether this therapy could be administered competently in outpatient clinics.[5] Twelve patients with OA associated pain in their knees were treated with PRP injections 3 times in 4 week intervals. Follow-up with the patients began 4 weeks after the last injection was placed. All 12 demonstrated improvement in their pain scores using an intermittent and constant osteoarthritis pain (ICOAP) questionnaire for knee arthritis, including two patients who reported complete resolution of pain at the four month follow up.[5] Outcomes were measured using the EURO-Qol Visual Analogue Scale (EQ-VAS) healthy utility which assess a patient's overall health from "worst possible" to "best possible" on a visual analog scale. In addition, patient specific goals were set to determine whether true mobility and function were achieved. The goals set by these patients included being pain free, walking normally without aids, decreasing joint stiffness, and preventing joint replacement surgery.[5] Eleven out of the 12 patients receiving PRP injections in this study reported success in achieving their specific goals at the four-month follow up. In addition, the average reduction in pain reported was significant at 29%, and the average health utility score increased significantly as well.[5] The chief finding in this study suggested that PRP injections are a viable treatment option to provide patients in an outpatient primary care setting. The study employed a limited amount of exclusion criteria which allowed more of a variety of patients to participate in the study however, the study only followed 12 participants. The

researchers suggest that due to the limited exclusion criteria the study may be easily implemented in a larger population. Major limitations with this study was the very small sample size of 12 participants with no loss throughout the study, participants were all of one single race, and the study did not use a control group. The study also reported no major adverse reactions occurring during the study due to the injections.[5]

In a study with longer follow up by Dhillon et al., 90 patients with degenerative changes in the knee were evaluated 24 months after treatment with PRP injections.[6] Both efficacy and durability of pain were examined. This study was an additional follow up investigation to the same group of participants who received PRP injections over a 12-month period. 91 patients participated in the initial PRP investigation, however one patient was lost to follow-up and did not participate in the 24-month evaluation. International Knee Documentation Committee (IKDC) subjective knee evaluation forms (knee-specific and patient reported) and EQ-VAS scores were used to measure knee symptoms. The results of these questionnaires revealed that all the parameters which initially improved, had worsened at the 24-month mark; IKDC scores fell from 67% to 59%. Despite the decrease in improvements over time, these scores were better than the patients' baseline scores before receiving any PRP injections. Furthermore, the study showed that the scores did not drop as much in younger patients nor in those with milder forms of OA. For most of these patients, the median duration of improvement was around the nine-month mark.[6] Although PRP injections were found to be a viable treatment modality for improving OA knee pain, the duration of PRP's benefits was limited. Notwithstanding this constraint PRP injections' maximal effectiveness averaged 9 months, and patients' symptoms improved vastly from their baselines. Major weaknesses in this study were the lack of control group and the omission of knee functional assessments.

In a meta-analysis by Zhang et al. WOMAC and VAS (visual Analog Scale for pain) scores were compared after PRP injections versus hyaluronic acid (HA) injections for the treatment of knee OA.[7] Three prospective observational and 10 randomized controlled trials with 1,520 participants in total were examined, with the majority of the participants (about 91%) in the early stages of OA. According to WOMAC scores, PRP injections reduced pain more effectively than HA injections at 6-month and 12-month follow ups.[7] VAS scores, however, showed no significant difference between the two types of injections at the three-month mark.[7] The findings from this meta-analysis revealed that while PRP injections were helpful, they may not have been be superior to HA injections. The absence of significance could have been due to differences among the studies in the quality of the preparations and the concentrations of the growth factors in the PRP injections. The most recent data from multiple resources were standardized in this review and found that overall PRP injections were beneficial. More studies are needed, however, to prove PRP's superiority to HA injections. The significant heterogenicity in each investigation's calculation and the wide variety of evaluation tools were limitations in this meta-analysis.

Finally, in a study by Joshi Jubert et al, a single PRP injection was found to be effective for reducing pain, and improving activities of daily living and QOL.[8] This study was a prospective, randomized, double-blinded clinical trial and focused mainly on patients with advanced OA. Sixty-five patients in total were randomized into either a PRP group (35) or a corticosteroid group (30), with only one participant lost from the PRP group.[8] Patients were evaluated using the VAS scale at one month to asses pain reduction. Additionally, the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Short-Form 36 (SF-36) at one, three and six months after the injection were used to measure function and quality of life. The VAS

scores decreased in both groups, but no significant difference was found between steroid and PRP injections.[8] The KOOS scores and the SF-36 results, however, were better in the PRP group compared with the corticosteroid group at all follow up intervals, showing that PRP injections gave patients better qualities of life.[8] While most of the studies dealt with early OA, this RCT's findings suggested that even in the later stages of OA, PRP injections can still be beneficial for patients who wish to avoid surgery. The limited sample size and hence the inability to rule out a type II error statistically, was a major limitation of this trial.

In addition to the success with PRP IA injections for knee OA, this therapy was shown to alleviate pain and improve function in patients with lumbar discogenic pain. Akeda et al. found that a single PRP injection in the lumbar spine produced favorable results in patients with discogenic low back pain.[9] In order to qualify for participation, patients must have been 18 years old or older and must have had established chronic low back pain with evidence of OA or degenerative joint disease by MRI, but without radiculopathies.[9] The results were remarkable despite the small sample size of 14 patients. With just one injection, 71% of the patients noted at least a 50% reduction of low back pain according to VAS scores.[9] Patients also experienced improvement of disability scores measured by Roland-Morris Disability Questionnaire (RDQ): 79% of patients had 50% or more improvement of function in their daily lives.[9] Two participants experienced temporary paresthesias in their lower extremities; however, those symptoms disappeared after 7 days and no other apparent adverse effects were noted.[9] This trial provided evidence that PRP injections were a safe, feasible and effective treatment option for patients suffering from lumbar discogenic pain. Thus, PRP could be a viable option for younger patients who are not ready and are generally not recommended for spinal fusion surgeries. An investigation with a large sample size would further elucidate the significance of these findings.

In another pilot study, Bhatia et al. included patients suffering from lumbar back pain for (with or without a history of radiculopathy) for at least four weeks who were 18-65 years old, had a positive straight leg raise test (SLRT), and were not responding to conventional treatments such as steroid injections, physical therapy, and spinal manipulation.[10] Patients were evaluated with VAS, Modified Oswestry Low Back Pain Disability Questionnaire (MODQ) scores, SLRT and neurology exams before and after the PRP injections.[10] Ten patients were followed for at least three months. Findings included gradual improvement of VAS scores, MODQ scores, and SLRT after the procedure. Within three months, all VAS scores were under five, MODQ scores were reduced by 30% and SLRT improved to 70 degrees.[10] Results were sustained for six months in more than half of the patients. Both back pain trials clearly demonstrated that PRP injections were efficacious in reducing pain as well as improving mobility in patients with low back pain.

In all the studies cited above, researchers concluded that PRP injections greatly benefit patients with osteoarthritis, specifically by reducing pain and improving function. PRP injections were shown to be superior to corticosteroids and hyaluronic acid for improving all the measured scores for pain, function and QOL. PRP injections were especially superior to all other interventions for achieving short term pain relief.

While research on PRP joint injections is still relatively new, some important questions still need to be answered. Future research to determine the long-term side effects of these injections should be planned. Other questions about PRP's efficacy necessitate further investigation. How long will the injections last? Do the injections lose efficacy over time? Is a specific amount of PRP injected into the joint more effective? Some researchers, even now, are starting to test the different growth factors in PRP to see which ones are the most effective and

which ones in combination with another could lead to better results. The final and most significant question of all is whether injecting PRP early enough in the OA disease process would not only slow progression but also potentially halt it and perhaps even reverse the damaging effects that OA has on joints. Examining the roles of growth factors and their concentration levels in PRP injections may help answer that question.

The major limitation to PRP is cost. Presently, it is extremely expensive and few clinics currently have the technology, education, and means to offer PRP as a treatment. These obstacles to making PRP readily available makes PRP inaccessible to the majority of patients who need it. Insurance companies are not covering any of the treatments since the research is still being done on whether it is an efficacious treatment option. However, with more research, over time the overall cost could decrease as insurance companies discover that PRP injections could be much less expensive than surgeries and just as, if not more, efficacious as steroid injections. Another limitation to PRP therapy is the time it takes to prepare and administer as this process can be lengthy. Patients who have been accustomed to quick in and out visits to receive a steroid injection may be surprised PRP injections may take up to an hour in the office. Another obstacle and limitation to PRP is the requirement for much more advanced equipment and training for this procedure. Providers and hospitals who want to offer PRP injections as a treatment option will have to buy expensive and specialized equipment in order to complete the procedure correctly and efficiently.

Conclusion

Platelet rich-plasma injections are a viable alternative therapy for patients who are suffering from chronic osteoarthritis pain and disability. PRP therapy appears to be safe and has

been shown to improve pain and disability scores at different joints in multiple studies. More research is needed to evaluate the true mechanism behind PRP injections. Longer term studies are needed to confirm the durability of the beneficial effects from these injections. Larger and different population samples are also needed to prove PRP injections will work for the general population and not just for a specific subset of patients.

For treating OA, PRP injections have already changed clinical practice. Clinicians can now use PRP injections as a conventional treatment before patients resort to a total joint replacement or spinal fusion surgeries; both of which are costly, not always effective, and like all surgeries have significant risks, dangers, and challenges. With further research PRP injections can become not only a conventional, but also a preferred treatment to help patients with osteoarthritis.

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