Spring 2023

Platelet-Rich Plasma vs Corticosteroid: Osteoarthritis Symptoms

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by

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A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

In partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2023

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Acknowledgment

I would like to thank my advisor and instructor Kristen Carr, MPAS, PA-C, DIPACLM for providing guidance and mentorship during this project. I would also like to thank Dr. Mark Yohe for his expertise and experience in osteoarthritic management and PRP injections. An additional thanks to Dr. Marilyn Klug who has an infectious enthusiasm for statistics and took time out of her schedule to help improve and discuss the research that was presented in this project. Lastly, I would like to thank my family for their unwavering support throughout the PA program.

Abstract

Osteoarthritis (OA) is a disease that hundreds of millions of people suffer from across the world (Palazzo et al., 2016). Currently, corticosteroid intra-articular injections are frequently administered to help with pain and inflammation related to OA (Pereira et al, 2015). A relatively new treatment option is Platelet-Rich Plasma (PRP) intra-articular injections. PRP injections use the patient's own plasma, injected into the affected joint space, to reduce inflammation and potentially improve both pain and functionality. This literature review will investigate whether the newer PRP injections relieve pain and improve functionality of OA patients better than corticosteroid injections. The literature review was conducted using the electronic databases PubMed and CINHAL from May 1, 2022 to October 1, 2022. Key words were platelet-rich plasma ± intra-articular ± osteoarthritis, corticosteroid + intra-articular ± osteoarthritis, corticosteroid + intra-articular, corticosteroid + intra-articular + osteoarthritis, and corticosteroid + osteoarthritis. In total, there were 8, 707 articles to screen. Articles were then evaluated and removed if they were duplicates, evaluated treatment for diseases other than osteoarthritis, compared other treatments against corticosteroids or platelet-rich plasma and/or were deemed as not answering the research question. Ten articles were selected as meeting the criteria for comparison studies. Current literature suggests that PRP injections more effective at relieving pain and improving functionality than corticosteroids for OA patients. More research is needed into ideal formulations of the PRP before it can be applied to widespread use and results may vary depending on which joints are being treated.

Key Words: Platelet-rich plasma, Osteoarthritis, Corticosteroids, intra-articular injections

Introduction

Osteoarthritis (OA) is a prominent degenerative disease that affects people across the world. OA is the result of narrowing of a joint space due to loss of cartilage and sclerosis of the bones that make up a joint (Pereira et al, 2015). OA causes pain and can significantly decrease mobility in patients leading to increase morbidity due to other disease processes, such as diabetes and cardiac abnormalities (Palazzo et al. 2016). In 2010, researchers estimated that approximately 10% of men and 13% of women in the United States had some form of osteoarthritis (Zhang et al, 2010). Other studies report the prevalence could be as high as 21.6% in the United States, with the World Health Organization (WHO) estimating 3.8% of the world's population has radiographically confirmed osteoarthritis (Palazzo et al., 2016).

Many researchers expect that the prevalence of patients with OA will continue to increase, in large part due to increasing obesity rates. Palazzo et al. suggested that for every five points increase in BMI over 30 there is a 35% increased risk of knee osteoarthritis (2016). One study found that as many as 24.6% of all new cases of knee osteoarthritis are found in obese patients (Silverwood et al., 2014). There are also several other factors that play a role in the prevalence of OA, such as increased rates noted in patients greater than 50 years of age as well as in patients with repetitive mechanical stress to their joints over several years (Palazzo et al., 2016). Other factors that have varying degrees of evidence to support the degree of risk for OA are genetics, gender, and socioeconomic status.

Statement of the Problem

With such high rates of occurrence, treatment options are frequently sought to help patients cope with symptoms, and possibly reverse the degradation of the joints. Surgical

intervention is often kept as a last resort, which can leave patients trying to find other ways to manage their disease. Oral medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) are an option but come with their own risks, such as gastrointestinal ulcers and renal damage, with chronic use. Injectable medications are frequently administered as well, including corticosteroid intra-articular injections and the newer platelet-rich plasma (PRP) injections. Injectable medications provide longer symptomatic relief per dosage and possibly improve functionality of the effected joint while carrying a lower risk profile (Pereira et al., 2015). PRP injections are relatively new to patients and providers and need to be evaluated as a treatment option in comparison to the previous corticosteroid intra-articular injections that have been the mainstay for injectable treatment for decades.

Research Question

In adults with osteoarthritis, do platelet-rich plasma (PRP) injections manage pain and improve functionality better than corticosteroid injections?

Methods

A literature review was conducted by searching the databases CINAHL and PubMed. Keywords and mesh terms were used to look for results related to osteoarthritis treatment with corticosteroid injections and/or platelet-rich plasma injections. The search terms included: platelet-rich plasma ± intra-articular ± osteoarthritis, corticosteroid + intra-articular and/or ± osteoarthritis. Searches were limited to publication dates between 2012 to 2022 with preference given to more current articles published within the past five years. Only full text articles and articles in English were counted. There were 5, 382 articles for platelet-rich plasma, 744 articles for platelet-rich plasma + osteoarthritis, 602 articles for platelet-rich plasma + intra-articular, and 366 articles for platelet-rich plasma + intra-articular + osteoarthritis. For the corticosteroid

studies, there were 649 articles for corticosteroid + intra-articular, 340 articles for corticosteroid + intra-articular + osteoarthritis, and 624 articles for corticosteroid + osteoarthritis. In total, there were 8, 707 articles to screen. Articles were then eliminated based on titles and abstracts if they were duplicates, evaluated treatment for diseases other than osteoarthritis, compared other treatments against corticosteroids or platelet-rich plasma and/or were deemed as not answering the research question. Ten articles were selected as meeting the criteria for comparison studies.

Literature Review

Theme 1: Efficacy of Platelet-Rich Plasma Injections in Reduction of Symptoms Related to Osteoarthritis in the First Three Months or Less Post Injection

Elik et al. (2020) conducted a double-blind, randomized, placebo-controlled trial to evaluate the effects of platelet-rich plasma (PRP) treatment on pain, functionality, quality of life, and cartilage thickness in patients with knee osteoarthritis (OA). The study inclusion criteria included: age of 50-75 years; history of pain during the previous year with a Visual Analogue Scale (VAS) >4; and grade 1-3 using the Kellgren-Lawrence classification system. Patients were excluded for the following reasons: any other rheumatoid conditions other than OA; systemic infectious disease or tumor; intra-articular (IA) injection to the knee or other physical treatment practices in the last three months; NSAIDs usage in the last seven days; any previous history of knee surgery; severe mental retardation; thrombocyte count equal to or less than 150,000/micro-liters; any bleeding disorder; Hepatitis B, C, or HIV; or any previous history of traumatic knee cartilage injury. The initial study population was 90, with 60 patients matching inclusion criteria. The patients were randomly divided into two groups of 30. One group received three 4mL PRP injections one week apart from each injection, while the other group received three 4mL of 0.9% saline with one week apart from each injection. Both groups had their blood drawn to keep

participants blinded. In addition to injections, both groups also received an exercise program to complete at home over the trial.

PRP was created by drawing 10 cc of blood into tube A with sodium citrate. The tubes were inverted slowly to ensure homogenizations. The tube A blood was spun in a centrifuge for 10 minutes at 2,000 rpm. Post centrifuge, three layers were created with the bottom layer being rich in erythrocytes, the middle layer being a buffy coat of leukocytes and thrombocytes, and the top layer comprised of plasma. The plasma and buffy coat were then transferred to Tube B and activated with calcium chloride. The B tubes were then spun in a centrifuge at 4,000 rpm for five minutes. The top layer of the B tubes produced 4 ml of PRP for use with the bottom layer having a small amount of clotting. The PRP was then tested with cell counts with the average thrombocyte count being 900,000-1,100,000 per mm and the average leukocyte count being 5,000-10,000/mm^3.

The injections were all done with the lateral approach while the knee was flexed at 90 degrees. The same physician did the injections for each patient. The physician was not blinded and at each injection the blood was drawn as stated above. The syringes were covered with a barcode paper to hide the physical differences of the substances injected. Patients were instructed to refrain from painful activities for two days post injection. NSAID use was not permitted, however paracetamol could be used if needed for pain. After the first two days post injection, the patients started an exercise program that focused on join mobility and range of motion. The program included stretching exercises that focused on the hamstring, rectus femoris, and gastrocnemius. Strengthening exercises were also included after the third dose of PRP or saline. The exercises were initially taught to the patients and the patients were then given a six-month

protocol to follow. The patients were asked about whether they performed the exercises as prescribed at each follow-up visit.

The VAS was used to assess pain. The WOMAC was used to assess functional state. The SF-36 was used to assess quality of life. Evaluations were completed at the beginning of treatment, at the first month following completion of injections, and at the sixth month following the injections. Femoral cartilage was measured by ultrasound at the beginning of treatment and at the sixth-month follow-up. The physician that evaluated the ultrasounds was blind to the treatments each patient received.

SPSS 22.00 was used to analyze the data. Descriptive statistics were represented as mean ± standard deviations, distribution of the frequencies, and percentages. Pearson chi-square test and Fisher's exact test were used to evaluate categorical variables. The Mann-Whitney U test was used if data did not follow a normal distribution. A p-value <0.05 was considered significant. Three of the initial 60 patients were excluded from the final results as the patients were not able to make their follow-up visits. The final break down was 30 PRP patients and 27 placebo patients. There was no statistical difference between the PRP group and the placebo group in terms of age, gender, BMI, additional diseases, or stage of OA. There was also no statistical difference in VAS scores prior to treatment in the two groups.

The VAS score showed improvement with both the PRP and placebo groups, however the PRP group showed greater improvement. The VAS scoring was broken into pain with rest, movement, and at night. The PRP injection group saw a reduction of pain at rest from 3.87 ± 2.14 to 1.80 ± 1.67 at the 1-month follow-up and a reduction of 1.20 ± 1.56 at six months ($p< 0.001$). The placebo group saw a change from 4.93 ± 1.68 to 3.67 ± 1.86 at one month ($p<0.001$) and 3.37 ± 2.32 at six months ($p<0.001$). The PRP group saw the largest decrease for in pain

with movement with a change from 7.10 ± 2.52 to 3.70 ± 2.20 at the first month and 2.80 ± 2.32 at six months ($p < 0.001$). The placebo group saw a change in pain from movement going from 7.74 ± 1.85 to 6.00 ± 2.86 at one month and 5.15 ± 2.60 at six months. ($p < 0.001$). The PRP group saw a change in pain at night from 4.23 ± 2.75 to 2.00 ± 2.01 at one month and 1.10 ± 1.35 at six months ($p < 0.001$). The placebo saw change for pain at night changed from 4.63 ± 2.32 to 3.18 ± 2.27 at one month and 3.19 ± 2.53 at six months ($p < 0.001$). The WOMAC score evaluated pain, stiffness, and physical function. The WOMAC score in the PRP group changed from 56.40 ± 18.71 to 35.77 ± 17.57 at one month and 24.87 ± 18.79 at six months ($p < 0.001$). The placebo group saw a smaller change in WOMAC scores with an initial score of 57.04 ± 15.12 decreasing to 43.94 ± 17.99 at one month and to 42.37 ± 18.64 at six months ($p < 0.001$). Table 5 from Elik et al. (2020) showed a percentage of decrement in WOMAC as 55.9% in the PRP group as compared to 23.3% in the placebo group. The SF-36 also showed superior change with the PRP group compared to the placebo group with a statistically significant reduction in all of the categories assessed. The categories were as follows: physical function; difficulty in physical role; pain; overall health; vitality; social isolation; difficulty in emotional role; mental health; physical health; and mental health again, evaluated with different questions. The placebo group saw some minor reduction in physical function, difficulty in physical role, and pain. A difference was noted in that the placebo group did not show a statistically significant reduction in the following: overall health; vitality; social isolation; difficulty in emotional role; or mental health (in both sets of questions). Table 4 from Elik et al. (2020) lists the individual data for each of the categories from the SF-36. Cartilage thickness showed no statistically significant differences in the medial, intercondylar, or lateral femur cartilage thicknesses throughout the study.

The double-blind, randomized control study showed that PRP had superior changes in nearly all categories evaluated. Participants in the study noted improvement in pain, functionality, stiffness, all the other listed categories the in VAS, WOMAC, and SF-36. The improvement was noted at the first month follow-up visit in all the categories and continued at the six-month evaluation. The only category that did not see a statistically significant improvement was the cartilage thickness ultrasound evaluation, which showed no benefit of PRP injections.

The authors did not declare any financial awards for the study nor any conflict of interests. The strengths of the study included the efforts the authors took to keep participants unaware of the therapy they received, including drawing blood from all participants as well as covering the syringes for visible differences. Another strength was that the study used several different surveys to evaluate symptoms post injection. A weakness of the study was the lack of data on the prescribed exercises that participants performed. Another weakness was that the authors did not list the cartilage thickness for participants in the study.

In a study published in 2021, Sun et al. investigated the efficacy of a single intra-articular PRP injection in patients with early knee osteoarthritis. The prospective study was done in an outpatient setting with care data collected from January of 2017 to December of 2017. The study's main objective was to evaluate mean VAS change from baseline at six months post injection. Evaluations were done at baseline and post injection intervals of one month, three months, and six months. Inclusion criteria for the study included: age 20-70, symptomatic knee OA for a minimum of six months despite NSAID use and/or physical therapy, average pain rated as a 30 out of 100 on the VAS scale, grade 1 or 2 knee OA per the Kellgren-Lawrence system. Potential participants were excluded for the following reasons: previous orthopedic surgery on

the spine or lower limbs, disabling OA of the foot or hip, knee instability, valgus/varus deformity, intra-articular injections in the knee within the last six months, infections or skin diseases around the knee, history of autoimmune diseases, hematological diseases, anticoagulated therapy, or any serious condition that researchers felt would limit results or assessments of the study.

Forty-six potential patients were identified prior to the study. Five of those 46 were excluded for not meeting the inclusion/exclusion criteria. Forty-one patients were officially enrolled. Three patients were unable to complete the study due to unlisted reasons not related to the study itself. Final data analyses looked at 38 patients with a mean age of 57.9 and an age range of 31-70 years. Mean BMI was recorded at 24.5 and radiographs showed Kellgren-Lawrence grade 1 for 15 people and grade 2 for 23 people.

The PRP was prepared by drawing 10mL of blood from each patient. The blood was placed in centrifuge using a Arthrex autologous conditioned plasma (ACP) kit. This kit results in low-leukocyte PRP. The blood was spun at 1500 rpm for five minutes. Researchers tested the resulting PRP prior to injection to ensure an approximately 2-3 times greater platelet concentration than baseline concentrations. Three milliliters of PRP was injected using a lateral approach. All injections were completed by the same provider. Patients were to refrain from NSAID use, glucosamine, or physical therapy during the trial. Acetaminophen was allowed for break through pain, although not within 24 hours of a follow-up evaluation. Any medications taken were to be recorded by the patient.

The VAS pain score ranged from 0 being no pain to 100 which was labeled as the worst possible pain. The study also looked at the WOMAC scale which evaluated pain, stiffness, and physical function. The Lequesne index was also used to evaluate severity of symptoms during

the last week. The Lequesne index measures pain, walking distance, and activities of daily living. All variables were evaluated as baseline prior to therapy, and at the one-, three-, and six-months intervals throughout the study. SPSS version 20.0 software was used for analyses of data collected.

The study showed that the VAS score had a statistically significant decrease from 45.6 ± 13 to 16.9 ± 13.4 at one month, 14.0 ± 13.1 at three months, and 15.5 ± 14.0 at six months. All scores had a p value less than 0.001. The WOMAC score saw a decrease from baseline of 29.9 ± 12.9 to 13.2 ± 9.0 at one month, 13.2 ± 8.9 at three months, and 14.9 ± 10.8 with $p< 0.001$ for all results. The Lequesne index followed a similar pattern with a decrease from a baseline of 7.6 ± 3.7 to 3.9 ± 2.6 at one month, 3.7 ± 3.0 at three months, and 3.9 ± 2.7 at six months with $p< 0.001$ for all. No infections or serious adverse events were recorded. Five patients experienced had unspecified minor adverse events that resolved without treatment within two days.

The data from this study shows evidence that PRP is an effective treatment option for patients with knee OA. The injection appeared to help patients with pain, functionality, and stiffness. The results showed a sustained relief up to six months, although improvement was noted earlier than that as well at the one month and three month follow-ups. With the reported adverse events being mild in nature and relatively low in frequency, PRP also appears to be a safe option for treatment.

This study used multiple, validated scoring methods to accurately determine the effects of PRP. The authors of the study attempted to maintain consistency amongst the patients by having one provider do all the injections. Follow-up visits were also conducted by the same provider. No conflicts of interest were reported. There were, however, some limitations to this study as

well. The sample size was relatively small, with no blinding or control methods to reduce potential bias.

Theme 2: Efficacy of Platelet-Rich Plasma Injections in Reduction of Symptoms Related to Osteoarthritis-Greater than Three Months Post Injection

A cohort study was completed by Altamura et al. (2020) to assess the efficacy of platelet-rich plasma intra-articular injections in patients with cartilage degeneration and osteoarthritis. Informed consent was obtained by all patients prior to the start of the study. Inclusion criteria were: unilateral symptomatic knee pain lasting at least four months, imaging via magnetic resonance imaging with findings of cartilage degeneration (Kellgren-Lawrence score of 0 but with detected chondropathy) or osteoarthritis, playing a sport at any level, (4) < or = 50 years old. Exclusion criteria were: age greater than 50, Kellgren-Lawrence score > 3, major axial deviation classified as five degrees valgus or varus, focal chondral lesion or osteochondral lesion, presence of any concomitant lesion causing pain or swelling in the knee, this included ligament or meniscal injuries, inflammatory arthropathy, hematological diseases, severe cardiovascular disease, infections, treatment with anticoagulants, NSAID use in five days prior to the blood being drawn, hemoglobin lower than 11 g/dL, and/or platelet count lower than 150,000/mm^3. A total of 49 patients were included in the study. Two patients were lost in follow-up due to unlisted reasons. The mean age was 41.1 and mean BMI was 25. Fifteen of the included patients had had a previous knee surgery and 12 had previously received hyaluronic acid or corticosteroid intra-articular injections.

The study was completed at the authors' outpatient orthopedics center. The blood used for the platelet-rich plasma (PRP) injections was quantified at 150 mL for each patient. Samples were centrifuged at 1480 rpm for 6 minutes and then at 3400 for 15 minutes. The centrifuged

blood yielded 20 mL of PRP which were then divided into 5 mL units. One unit was sent to lab for quality control testing and the other three were placed in storage at -30 degrees Celsius to be used later. When needed, the units were reactivated with 10% calcium chloride. Patients received three weekly intra-articular injections. Post injection, the patients were instructed to use ice to relieve pain and avoid high impact activities. Return to activity was encouraged as tolerated. Evaluations were completed at two-, six-, twelve-, and twenty-four-month intervals after the last injection. The evaluations used the International Knee Documentation Committee (IKDC) subjective score, EuroQol visual analog scale (EQ-VAS) and Tegner score. Additionally, all patients were also asked about their return to sport at any level as well as return to sport at the previous level prior to symptom onset. All data was expressed in terms of mean and standard deviation. Categorical data was expressed as frequency and percentages. The Spearman Rank Correlation was used to evaluate any correlation between age or BMI and the recorded scores. For all tests, $P< 0.05$ was considered significant. SPSS v.19.0 was used to evaluate the data.

No major adverse events were reported. A statistically significant improvement was noted in all observed scores. The IKDC subjective score improved most significantly from 59.2 ± 13.6 to 68.0 ± 13.9 at two months, 69.9 ± 13.8 at six months, 70.6 ± 13 at twelve months, and 76.7 ± 12.5 at twenty-four months with a $p<0.0005$ for all. The EQ-VAS score showed improvement from a basal score of 73.6 ± 11.9 to 80.6 ± 11.6 at two months ($p=0.004$), 82.2 ± 9.1 at six months ($p< 0.0005$), 81.0 ± 10.4 at twelve months, and 85.5 ± 8.6 with $p<0.0005$ compared to basal at twenty-four months. The Tegner score evaluated activity level and showed a change from a basal of 3.6 ± 1.4 to 4.4 ± 1.4 ($p=0.002$) at two months. Scores then remained stable without significant change until the 24-month follow-up with a score of 4.8 ± 0.9 $p<0.0005$. For return to sport (RTS), 36 patients (76.6%) returned to some kind of sport activity,

whereas 23 patients (48.9%) returned to the same level of activity that they were doing prior to symptom onset. The Spearman correlation showed that age and BMI did not significantly change the scores. The Mann-Whitney test showed that previous surgery and previous intra-articular injections did not significantly change the scores. A lower Tegner score pre-treatment was associated with a higher RTS at any level ($p=0.024$) and at the same pre-symptom level ($p<0.0005$). Overall, the findings of this study showed a significant clinical improvement in sport-active patients that suffered from OA. However, only about half of the participants were able to return to the same level of sport activity before onset of symptoms.

The authors denied any potential bias for the study. Strengths of this study include using both subjective pain scales that are standardized across the world, as well as objective data that addressed return to sport activity level. Additionally, a constant PRP harvesting method was used providing consistent concentrations for each person. A potential limitation to the study is that pain medication use was not explicitly recorded during the trial itself.

A randomized, block-randomized, double-blinded, placebo-controlled clinical trial was conducted by Paget et al. (2021) to determine PRP injections effect on symptoms in patients with ankle osteoarthritis. The study was conducted at six sites across the Netherlands. Eligibility for the study required participants to be older than 18 years of age and have a score of at minimum 40 for pain due to ankle osteoarthritis on the Visual Analog Scale (VAS). Radiographic imaging was also required to confirm at least grade 2 OA on the van Dijk classification scale. Potential participants were excluded from the study if they had any of the following: injection therapy for ankle OA within the past 6 months; signs of concomitant OA of one or more other major joints of the lower extremities; or if they had underwent previous ankle surgery for either OA or osteochondral defects within the past year prior to the study. In total, 100 patients were selected

with a computer randomized program dividing the groups into PRP or Placebo. The study ended with 52 participants in the placebo group and 46 in the PRP group. Two participants were lost to follow-up from the PRP group, which had started with 48 participants.

The procedures for injecting PRP as well as the placebo were standardized and performed by the same provider. The provider was unaware of which patients received which injection and lab assistants placed the syringes in sheathes to cover the physical differences between the placebo and PRP. The placebo group received 0.9% normal saline 2 mL and the PRP group received 2mL of PRP. The PRP was prepared by drawing 15 mL of blood and spinning in a centrifuge for five minutes. The researchers did not add any other substances to the injections. Placement of the injection was identical for each participant using anatomical landmarks and ultrasound guided injection. No local anesthetic was used. Patients were instructed to avoid heavy or repetitive activities post injection for 48 hours. They were also advised to avoid NSAIDs for the year of the study. A second injection for both groups was done six weeks after the first injection following the same procedures listed above.

The primary outcome measured in the study was the American Orthopedic Foot and Ankle Society (AOFAS) score over 26 weeks of follow-up. The AOFAS score ranges from 0-100 with higher scores indicating less pain and better function. The AOFAS was given to patients at baseline as well as post injection at six, twelve, and twenty-six weeks. All participants were given the test by the same physician who traveled to the various research sites.

Data collected was evaluated using a general linear model. The data was grouped together with all PRP participants in one group and placebo participants in the other. The researchers were blinded to which data set belonged to each group. Statistical analyses were

done by the computer program IBM SPSS version 26. A 2-sided P < or = to 0.05 was considered statistically significant.

The baseline AOFAS for the PRP group had a mean of 63 with the placebo group having a mean of 64. Primary outcome of AOFAS at 26 weeks showed improvement by 10 points in the PRP group (95% CI, 6-14) and 11 points in the placebo group (95% CI, 7-15). The difference was -1 point (95% CI, -6 to 3) with p = 0.56. All other measurements were statistically insignificant and can be found in Figure 3 of the study (Paget et al., 2021). The results of the study do not suggest any significant benefit in the use of PRP for treatment of ankle osteoarthritis as there was no significant improvement of pain or function noted at six weeks, twelve weeks, or twenty-four weeks.

Strengths of this study include the placebo-control and blinding of participants and researchers. The researchers did conduct a survey to participants post injection to see which injection they believed they had gotten. 33 patients (69%) in the PRP group and 36 patients (69%) in the placebo group believed they had gotten a PRP injection after the first injection. 29 patients (60%) in the PRP group and 36 (69%) in the placebo group believed they had gotten the PRP injection after the second injection. The standardization of the injections for all participants allowed for limited variation in technique that could affect scores.

The study did also have some limitations. The researchers acknowledge they were unsure of what concentration of PRP they should use. They decided to use leukocyte-poor PRP, although it does not look like the PRP from each participant was tested to ensure standardization across all the PRP patients. There are numerous studies pointing to leukocyte-rich PRP showing more effectiveness as shown in McLarnon and Heron's (2021) meta-analysis. Additionally, the

study started with unequal participants in the two groups being studied which could affect scoring, even more so as the PRP group started with fewer participants and then lost two more.

Theme 3: Efficacy of Glucocorticoid Injections in Reduction of Symptoms Related to Osteoarthritis- Three Months or Less Post Injection

A systemic review and meta-analysis were conducted by Zhong et al. (2020) to assess the efficacy of Intra-articular Steroid Therapy (IAST) in patients with hip osteoarthritis. The literature search included Medline, EMBASE, and Web of Science with date range being from inception to May of 2019. Researchers used "hip osteoarthritis AND intra-articular injection AND steroids OR methylprednisolone OR triamcinolone OR betamethasone" as key words during their search. No limits were placed on language or age. Randomized controlled trials, noncontrolled clinic trials, and cohort and case-control studies were all included. Articles included for selection had to report on patients' pain from hip OA, with the hip OA being diagnosed by ACR criteria and/or radiographic evidence. The included articles had to have intervention groups in which IAST was used as a treatment. Articles were excluded if they were animal trials, protocols, reviews, and/or if they did not have measurable data to compare results.

The search yielded a total of 301 potential articles. Two hundred forty articles were removed by review of their clinical trial and duplication of other articles. Thirty-eight articles were removed based on information from their title and abstract. Of the remaining 23 articles, 12 were excluded for not having pertinent information. One additional article was found by review of references from the studies, which left 12 total articles/trials to be included. These 12 studies had a total of 1,504 patients to evaluate.

The pain measurements for the various studies included baseline levels and scores at intervals throughout the length of the studies. The duration of the study, number and intervals of

follow-up evaluations, losses to follow-up, and any reported side effects were all extracted and summarized from the articles. The type of pain scale used varied in the studies that were reviewed so researchers converted scores using a standardized mean difference. The intervals of follow-up also varied, so the studies were grouped into outcomes at 1-2 weeks, 3-4 weeks, and 8-12 weeks with anything greater than or equal to eight weeks being considered long term. This left two studies reporting data for 1-2 weeks, four studies reporting data for 3-4 weeks, and five studies reporting data for 8-12 weeks.

Results of the study data are as follows: 1-2 weeks SMD (95% CI): -1.58 [-3.42,- 0.26] p= 0.09, I^2= 93%; 3-4 weeks SMD (95% CI): -1.93 [-3.34, -0.52] p= 0.007, I^2=95%; and 8-12 weeks SMD (95% CI): -1.77 [-2.94, -0.61] p= 0.003, I^2=94%. Results of this meta-analysis and systematic review show that corticosteroid injection is effective at reducing pain, however after eight weeks the effects begin to decline as the studies progressed to the 12-week interval.

There are limitations to this analysis. Standard practice for many providers is noted to offer injections every three months for patients with OA. This meta-analysis did not look at the efficacy or risks associated with repetitive corticosteroid injections. The authors also included a variety of different steroid medications, with no standardization in dosage, injection method, nor added analgesics. However, throughout the analysis the authors did try to convert data to a standard measurement for comparison. The authors also listed the differences amongst each of the studies such as population size, identification of the steroid that was used, length of the study, and the summarized data for each individual study (Figure 2). The authors denied any potential conflicts of interest and all funding was reported to be independent so as not to influence the results.

Matzkin et al. (2017) performed a prospective cohort study to evaluate the efficacy of intra-articular corticosteroid injections in knee osteoarthritis. Two academic centers were selected to enroll participants with the following inclusion requirements: age greater than or equal to 40; radiographic evidence of OA; and a history of unsuccessful treatment with anti-inflammatory or acetaminophen for pain relief. Participants were excluded from the study if they had any of the following: previous intra-articular injection to knee within the last six months; previous total knee arthroplasty; narcotic medication use; pregnancy; systemic disease diagnosis; metabolic disease; and/or pain disorder such as complex regional pain syndrome or fibromyalgia.

The initial count of potential participants who signed informed consent was listed at 144. Thirty-one patients were unable to complete the study with two participants undergoing knee surgery, 25 patients lost to follow-up, and four participants who developed systemic disease and were asked to leave. Thirteen patients were excluded from the results as they had bilateral injections, which left a total of 100 patients included for study analysis. The mean age of participants was 61.2, the mean BMI was 31.2, and gender differences were not listed.

The primary outcome to be measured was the overall WOMAC score which ranged from 0 to 85. A higher score meant higher levels of pain, disability, and/or stiffness. The primary interval for this measurement was selected as three months. Visual numeric score (VNS) was used to evaluate pain as a secondary outcome. Patients were evaluated at baseline and post injection at three weeks, six weeks, three months, and six months. $P < 0.05$ was considered significant. The researchers also used a minimal clinically important difference (MCID) for WOMAC and VNS scores. The MCID cutoff for WOMAC was 21.7% based off previous studies as listed by Matzkin et al. (2017). The MCID for VNS was a 27.9% reduction calculated

by raw change divided by baseline score and multiplied by 100. Analysis was completed by SPSS version 22.0.

Participants received one intra-articular injection of triamcinolone with a dose of 10 mg or 1mL combined with 4 mL of 1% lidocaine for a total fluid injection of 5 mL. Two orthopedic surgeons did the injections for all participants. The procedure was done with an antero-lateral approach while the knee was bent at 90 degrees of flexion.

VNS scoring showed a decrease in pain by 23.9% at three weeks, 26.9% at six weeks, 20.7% at three months, and 17.1% at six months $p< 0.05$ for all expect at six months where $p=0.0114$. These values did not reach the MCID needed for clinical significance of 27.9%. WOMAC scores showed improvement in pain, stiffness, and functionality with $p<0.001$ at all times evaluated. WOMAC scores showed a 34% improvement at three weeks, 37.6% at six weeks, 34.4% at three months, and 40.2% at six months.

The results of this study show that corticosteroid intra-articular injections are a suitable option for treatment of knee osteoarthritis. The injections improved pain, function, and stiffness for participants with both a clinically significant and statistically significant result. The VNS scores were statistically significant, and it is important to note that the VNS scores showed no statistical significance in benefit at six months. The VNS score did not show a large enough decrease in symptoms to be considered clinically relevant. Both scoring systems show that corticosteroids are effective as quickly as three weeks post injection with some sustained benefit possibly up to six months. After the initial decrease in symptoms at three weeks, scores stayed relatively stable and in VNS scoring it appears as though the corticosteroid benefits started to decrease at the three-month mark. WOMAC scores showed a similar pattern, although there was another small improvement of symptoms when going from three months to six months. Obesity

also appeared to affect results as those with a BMI greater than 30 saw less improvement than their counterparts with a BMI less than 30. This difference was significant at baseline (p=0.003), six weeks (p= 0.010), and at three months (p= 0.009).

This study used multiple scales to assess pain which strengthened the results. Additionally, the WOMAC and VNS scales are standard scales used to assess pain in many other studies related to osteoarthritis. This study is limited in that the dose of triamcinolone was relatively low and included an analgesic agent in the injection. There were also many participants lost to follow-up, with an attrition rate of 21.5%. Researchers theorized that it was possible that the patients who did not return did so because they did not benefit from treatment, and this could result in a selection bias in the study. There was also no placebo control with the study, so it is possible there was a placebo effect in participating patients.

Theme 4: Efficacy of Glucocorticoid Injections in Reduction of Symptoms Related to Osteoarthritis Greater than Three Months Post Injection

A randomized control study completed with a placebo control was conducted by Conaghan et al. in 2017 to assess the effectiveness of triamcinolone acetonide extended-release injections for osteoarthritis. There were three substances injected: a saline solution-placebo, triamcinolone acetonide extended-release (FX006), and a triamcinolone crystalline suspension (TAcs). Average daily pain (ADP) was used on a scale of 0-10 with 10 “as bad as you can imagine” and 0 being no pain to assess effectiveness of each treatment. There were 486 participants enrolled and randomized treated from the following countries: The United States, Canada, Australia, New Zealand, China, and unlisted countries throughout the European Union. Inclusion criteria included men and women age >40 with symptomatic knee osteoarthritis lasting > or = to six months prior to the screening for the study. The patients had to have osteoarthritis

with a Kellgren-Lawrence grade of 2 or 3 assessed via radiograph. Participants also had to have reported pain >15 days in the previous month, a 24-hour ADP-intensity score of > or = to five and < or = to nine for greater than five days during the week prior to the screening. Exclusion criteria included any knee arthroscopic or open surgery within 12 months of screening. Participants also could not have received a FX006 injection or other intra-articular corticosteroids within the last three months, intramuscular corticosteroid within the last month, intra-articular hyaluronic acid within the last six months, and/or any other intra-articular investigational drug/biologic within the last six months. Diabetic patients with A1C greater than 7.5% were also excluded from the study.

The intervention given was a single intra-articular injection of FX006 with 5mL of fluid injected at a dose of 32 mg. The saline placebo was also 5mL of fluid. The TAcs were dosed at 40mg (1mL). The dosages were selected to represent current standard of care at time of the study. Assessors were not aware of who received which injection. Similarly, patients were not aware of which injection they received. The injector was aware of each substance being injected. The injector could also choose a medial or lateral approach and position the knee how they desired. Numbing agents were limited to ethyl chlorine or subcutaneous lidocaine only. The participants were randomly selected into a 1:1:1 ratio of the three possible injections. Assessments were done at 4, 8, 12, 16, 20, and 24 weeks. ADP intensity was recorded daily from 4:00pm-12am. Participants were also limited to paracetamol or acetaminophen (< or = 3,000 mg/day; 500mg tablets) for rescue pain throughout the study and prior to once they signed the informed consent forms.

The primary end point of the study was the LSM change from baseline to week 12 in weekly mean ADP-intensity scores for FX006 compared to the saline-solution placebo.

Secondary end points included change of area-under-effect (AUE) in weekly mean ADP-intensity scores in participants given FX006 compared with the placebo at week 12, FX006 compared with TAcs at week 12, and FX006 compared with placebo at week 24. The data was analyzed with a longitudinal mixed-effects model for repeat measures using observed data, with fixed effects for treatment group, study week, treatment-by-week interaction, study site, baseline pain, and a random patient effect.

Of the 486 patients enrolled in the study, 161 received FX006, 163 received the saline solution placebo, and 162 received TAcs. Two patients were neither treated nor included into the analysis set or safety populations. 91.2% of the patients (443) completed the study through the 24 weeks, 8.8% (43) did not complete the full study, and 3.3% (16) discontinued the study prior to week 12. The mean age of the patients was 62 years old, ranging from 40-85. Females made up 61.2% and approximately 50% of all were obese with a BMI > or= to 30.

The results showed approximately 50% improvement with Fx006 compared with the saline placebo. There was a LSM change in weekly mean ADP-intensity scores from baseline to week 12 of a -3.12 reduction compared with -2.14 of the placebo group. There was a 95% CI -0.98 (-1.47 to -0.49) with p< 0.0001. Secondary outcomes showed AUE weeks 1-12 with FX006 -247.3 compared to TAcs -145.3 with LSM difference 95% CI -102.0 (-136.8, -67.3) p<0.0001. The mean ADP change from baseline to week 12 with FX006 was -3.12 when compared to TAcs -2.86 with LSM difference 95% CI -0.26 (-0.74, 0.23) p= 2.964. Finally, AUE weeks 1-24 with FX006 was -432.5 compared to the placebo with -297.0 and a LSM difference 95% CI -135.5 (-205.9, -65.2) p=0.0002. Overall, participants showed a greater reduction in pain with the FX006 injection.

Strengths of the study include the large number of participants that remained in the study throughout the entire 24 weeks. The researchers also maintained a thorough blind study so that neither the assessors or the participants knew who had what injections. Weaknesses of this study include the potential bias of the authors, who are employed by the company that makes FX006. The authors did bring in a third-party reviewer to review the study material prior to publication to mitigate any potential professional bias. Another weakness was the differences in volume injected when looking at 5mL for both the FX006 and placebo injections compared with the 1mL of TAcs. Progression of osteoarthritis by joint space narrowing was also not measured as part of this study. The results reported by patients are also subjective as the pain scale is what they perceive and not standardized. Additionally, this study looked at a single injection as compared with multiple injections over time.

Nunes-Tamashiro et al. published a study in 2022 that compared triamcinolone hexacetonide intra-articular injections to saline injections as well as PRP injections. The study was setup as a controlled, randomized, double-blind study. To be included in the study, patients had to be older than 40 years of age and less than 85. They had to have a symptomatic diagnosis of osteoarthritis in the knee with radiographic Kellgren-Lawrence grade II or III. The patients were required to have pain for greater than three months that interfered with function on most days of the week. Potential participants were excluded if they had any of the following conditions: cutaneous knee injury; intra-articular injection with corticosteroids or hyaluronic acid within the last 6 months in the knee; use of any corticosteroids within the last 30 days; inflammatory arthritis; oncologic disease; previous surgery; pregnancy; severe clotting disorder; bacterial infection of any kind; antiplatelet medication use; anti-inflammatory medication within the last 14 days; and/or thrombocytopenia.

Initially, 287 patients were evaluated for eligibility. One hundred eighty-seven of those patients were excluded for not meeting inclusion criteria and 10 were excluded for thrombocytopenia. Thirty-three patients were randomly placed in the triamcinolone group, 33 in the saline group, and 33 in the PRP group. Forty-six percent of the patients had Kellgren-Lawrence grade II and 54% had grade III osteoarthritis. The authors stated there was no significant difference between the three groups in terms of gender, ethnicity, mean age, mean BMI, or mean symptom time. Overall, the study had 90% female patients, a mean age of 67, mean BMI of 29.68 and a mean symptomatic time of 8.13 years. Further breakdown of demographics is noted in Table 1 of the study.

Primary outcome of the study was to evaluate VAS pain on movement on a scale of 0-10. Secondary outcomes included: VAS pain score at rest; WOMAC survey assessing pain, stiffness, and function; percentage improvement from 0% to 100% rated by the patients themselves; and radiograph changes as assessed by blinded radiologist. SPSS version 15.0 was used to perform analysis of the data.

The results of the study showed that the triamcinolone injections had a change from baseline with VAS pain in movement from 6.1 ±2.2 to 2.8 ± 2.8 at 12 weeks and 3.5± 3.1 at 52 weeks. The saline group showed a change from 5.6 ± 2.2 at baseline VAS movement to 3.5 ± 2.8 at 12 weeks and 3.5 ± 2.8 at 52 weeks with an intergroup p= 0.433. At rest, the triamcinolone group had a change from baseline of 4.2 ± 2.7 to 1.7 ± 2.9 at 12 weeks and 1.3 ± 1.8 at 52 weeks. The saline group saw an at rest VAS change from 4.2 ± 2.9 at baseline to 2.2 ± 2.8 at 12 weeks and 1.7 ± 2.3 at 52 weeks with p=0.641 between all three groups. Researchers did not list the p values independently for each group, making it difficult to determine if these findings are independently statistically significant.

The WOMAC scale results showed that the triamcinolone group had improvement from 5.29 ± 2.06 to 2.38 ± 2.18 at 12 weeks and 2.91 ± 2.73 at 52 weeks. The saline group had a change from 5.25 ±1.97 to 3.12 ± 2.30 at 12 weeks and 2.62 ± 2.15 at 52 weeks. The inter-group p value for the WOMAC total scores was p= 0.003 making it statistically significant as a group. The Kellgren-Lawrence scores for the triamcinolone saw a 41.17 % increase to grade III from grade II with p=0.003 at 52 weeks. The saline group had a 76.47% increase to Kellgren-Lawrence grade III osteoarthritis with p< 0.001. Tables 2, 3, and 4 in the article present the PRP data as well as further data on the saline and steroid groups.

The results of this study appear to indicate that triamcinolone may improve pain and function better than a saline placebo. However, the inter-group p values were not statistically significant with the VAS scale. The WOMAC system did see a statistically significant improvement in scores in favor of triamcinolone over the saline placebo. One of the most important findings of this study was a slower progression in osteoarthritis via radiographic imaging in the triamcinolone group compared to saline.

Limitations of the study include relatively small sample sizes for each of the groups assessed, as well as a lack of p values listed for each group independently. The authors do appear to draw conclusions from values that are statistically insignificant, making it difficult to ascertain the results without going through the data itself. The strengths of the study lie mostly in its comparison of PRP and triamcinolone to a placebo saline group. Although the PRP groups data was not listed for this document, the results were similar to the corticosteroid group with less progression in radiographic osteoarthritis.

Theme 5: Direct comparison of platelet-rich plasma intra-articular injections compared to corticosteroid intra-articular injections

A single-center prospective randomized controlled study with a one-year follow-up visit was completed Elksniņš-Finogejevs et al. in 2020 to assess the efficacy of platelet-rich plasma intra-articular injections compared to corticosteroid intra-articular injections. The study focused on osteoarthritic patients, specifically patients with knee osteoarthritis (OA). Inclusion criteria for the study included: age over 55 years, chronic pain history, swelling, and/or reduced range of motion in the knee joint. Clinical and radiological confirmation of knee's OA with a Kellgren-Lawrence grade of II-III was verified via x-ray with anteroposterior approach and lateral approach. Exclusion criteria included: post-traumatic knee OA, pregnancy, breastfeeding, oncological diseases, endocrine diseases, auto-immune diseases, acute or chronic infectious disease, blood clotting disorders, previous interventions of the knee joint (including punctures, blockades, arthroscopy), previous consistent hormonal therapy, or NSAID treatment within 10 days prior to the study. A total of 40 patients were selected for the study, with 32 females and eight males. The patients were randomized using the computer program Randomized for Clinical Trial into 1:1 groups with 20 patients receiving PRP injections and 20 receiving corticosteroid injections. Each patient received one injection of their assigned medication.

Platelet-rich plasma was prepared using the Hy-Tissue PRP system. Eighteen milliliters of peripheral blood was collected and 2mL of 3.8% sodium citrate was added. The 20mL of citrated blood was centrifuged at 1800 rpm for eight min using a Duografter II centrifuge. This resulted in 8mL of pure PRP solution that would be used for the injections. Patients in group 1 received the 8mL dose of PRP and the group 2 participants received 1mL of triamcinolone acetonide mixed with 5mL of 2% lidocaine. The injections were performed using sterile technique, without any local or general anesthesia. A 20-G x 2.75 70mm needle was used. The anterolateral approach was universally used for all patients. Echographic control was used to

allow for direct visualization and proper needle placement for the injections. All follow-visits were completed by an evaluator blinded to the treatment. NSAID use was prohibited for 10 days following the injections. Patients were permitted to perform their normal daily activities without restriction.

The change in pain from baseline was measured by the Visual Analog Scale (VAS) score at 1 year (V1), which was the primary goal of the study. The VAS pain score was completed by the patient and ranged from 0-10 points. Secondary outcomes included determining the International Knee Documentation Committee (IKDC) score and Knee Society Score (KSS) at any time in the study. An average of 7.3 for the VAS score was assumed with the control group with a standard deviation of 1.6. For the study, this meant that a reduction of 1.5 points in the treatment group with a power of 80% and 2-sided significance level of 0.05 would require inclusion of a total of 36 patients. Forty patients were required due to possible dropouts during the study. Categorical variables were described by percentages and frequencies. Continuous variables were described by means, standard deviations, and a 95% confidence interval of the mean. For all tests, $p<0.05$ was considered significant.

For final analysis, a total of four patients were excluded. One patient from the PRP group had presentation of an unrelated autoimmune disease which was an exclusion criterion. Three patients that were in the corticosteroid group were unable to complete the study due to undergoing an arthroplasty procedure. Clinical results showed improvement in both corticosteroid and PRP injection at the one-year mark. However PRP had a significantly higher mean change from baseline with PRP being -3.1 ± 2.0, -52%; CS -0.8 ± 1.8, -14% with p=0.0002. PRP and CS also both worked quickly to relieve symptoms with the VAS change mean from baseline to one week being -2.8 ± 2.3, -47% for PRP and -3.4 ± 1.2, -58% with

$p<0.0001$. Maximum functional improvement and better patient expectation, satisfaction, and activity levels were observed after 15 weeks for the PRP group with the mean change from baseline of 41.1 ± 13.6, 112% and 30.2 ± 11.7, 51% for IKDC and after five weeks for the CS group with a mean change from the baseline of 33.7 ± 13.5, 111% and 29.4 ± 12.8, 55% for KSS.

Overall, the authors concluded that both PRP and corticosteroid injections can provide improvement in pain up to five weeks and function up to 15 weeks. However, the results showed that PRP injections provide a more sustained and significant improvement in both pain and function. Potential limitations include the lack of double blinding for this study. The authors stated that they felt double-blinding was not possible because the PRP injections required blood draws prior to injection and the CS group would not require that. Additionally, the authors noted that the visible differences of PRP vs corticosteroids prevented blinding of the clinicians doing the injections. There were also relatively small sample sizes evaluated. Magnetic resonance imaging (MRI) also could have potentially made the study stronger due to its ability to determine the effect of PRP on the actual cartilage tissue. Strengths of the study include the use of three different rating scales to be completed by the patients. This provided additional data to compare and strengthened the argument that PRP injections provided more sustained improvement. There was no funding received for this study and the authors denied any potential conflicts of interest.

McLarnon and Heron (2021) conducted a systemic review and meta-analysis comparing intra-articular (IA) platelet-rich plasma injections (PRP) to corticosteroid injections (CS). The primary aim of the study was to investigate the difference between PRP and CS in symptomatic management of adults with knee OA. Secondary goals included identifying the effectiveness of one IA PRP injection compared to multiple IA PRP injections for one course of treatment. The

other secondary goal was to evaluate whether Leukocyte Rich PRP (LR-PRP) was more effective than Leukocytes Poor PRP (LP-PRP) for OA symptomatic treatment.

McLarnon and Heron used MEDLINE, EMBASE, Web of Science, and Scopus to find articles for review. They enlisted the aid of an unnamed medical librarian to assist with search parameters. The MESH terms included knee and platelet rich plasma, with other search terms not reported. There was no limit on timeframe or language. Studies that directly compared PRP and CS for symptomatic knee OA were screened by both authors for additional references. Inclusion criteria included: age over 18 for participants, symptomatic knee OA, and a direct comparison of PRP versus CS for intra-articular injections. Exclusion criteria was: age of participants less than 18 years, studies that did not directly compare PRP and CS, and studies that used co-interventions alongside PRP or CS. Titles and abstracts were evaluated by the authors of this study and those that did not meet the criteria were eliminated. The authors also excluded studies that did not use the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), or the visual analog scales (VAS) for pain assessment of the knee osteoarthritis. Those scoring systems are the most commonly used pain scales for assessing osteoarthritis across the world and provide some standardization for comparing outcomes across multiple studies. The authors were also blinded to the initial systemic review as they were not privy to each other's opinion on articles as they screened them. At the end, they discussed the controversial studies and made a joint decision on inclusion or exclusion.

Search results yielded an initial 1,566 potential articles. Five hundred seventy-nine articles remained after duplicates were removed. The titles and abstracts were then screened, and 567 articles were removed for not meeting inclusion criteria. Of the 12 remaining articles, two

were excluded as they were conference abstracts only and the authors could not be reached for further information. One article was removed after speaking to the author of the article and McLarnon and Heron felt it did not meet their criteria. The last article to be excluded was removed because the full text could not be purchased or accessed. In total, eight studies were included for meta-analysis. The difference in mean with the corresponding standard error was extracted from each study as measured by the VAS, WOMAC, and/or KOOS. The scores were also sorted into the timeframes for which they were assessed at, for example, all scores for VAS at six months were put together. A random effects model was used to obtain a pooled standardized mean difference with a 95% confidence interval. The Chi-squared test for heterogeneity was also used. All statistical analyses were completed using Review Manager 5.4.

The eight combined studies had 648 patients with 206 males (32%) and 442 females (68%). The mean age was 59 years. The studies used Kellgren-Lawrence grading system to determine the severity of the OA with 0.2% grade I, 45% grade II, 45% grade III, and 9% grade IV. The mean BMI of the patients was 28.4 out of the six studies that reported BMI. Five of the studies used WOMAC as the main outcome score, two studies used KOOS, and seven of the eight studies included VAS scores. The studies recorded results at different times with four studies reporting outcomes at one month, two studies at two months, five studies at three months, seven studies at six months, one study at nine months, and two studies at twelve months. Three studies used multiple PRP injections. Five studies use LR-PRP and three studies used LP-PRP. None of the studies allowed participants that had knee injections within three months of the study or systemic diseases that affected the joints or blood. Three of the studies were conducted in Europe, one study in South America, and four studies were done in Asia. There was no standardization to the preparation of PRP which resulted in a variety of concentrations and

methods used for the PRP injections. In four of the studies there were no dropouts. The remaining four studies had a mean attrition rate of 11% for the CS group and 2.25% in the PRP group. The reasons for attrition were all listed in the individual papers. Four of the studies reported adverse effects which were all self-limiting and considered mild by the researchers. None of the studies had an apparent sponsorship bias or publication bias.

The 6-month follow-up reports showed that the mean score in the PRP group was 0.78 SMD ($p<0.005$) lower than in the CS group with a reported 95% CI 0.12, 0.90. The WOMAC showed an individual reduction of -9.51 (-15.20, -3.83) with $p=0.05$ and the VAS showed an individual reduction of -0.97 (-1.94, 0.00) with $p=0.05$. Only one study showed results at nine months with a WOMAC additional reduction score of -8.04 (-10.19, -5.89) $p<0.00001$. The two studies that had results at 12 months did not have statistically significant results, although they did trend towards PRP. Kellgren-Lawrence (KL) grading was also compared to show effectiveness of PRP versus CS at different stages of OA. There was a non-significant benefit of PRP at KL grades 1-2 in two studies. Four studies showed a significant reduction of 1SMD in KL grade 2-3 with $p<0.00001$. LP-PRP showed a reduction of 0.61 (-0.92, -0.29) SMD with $p= 0.00002$ when compared to CS. LR-PRP had a SMD reduction of -0.98 (-1.79, -0.17) with $p=0.02$. A single PRP injection had a SMD reduction of -0.52 (-1.11, 0.07) $p= 0.08$ when compared to CS and three PRP injections had a reduction of -0.94 (-1.31, -0.58) with $p<0.00001$.

The statistical results show a greater improvement in PRP injections compared to CS in the primary and secondary goals of the study. The most pronounced benefit of PRP over CS is from six to nine months and the benefit seems to be seen mostly in KL grades 2-3. Three injections of PRP also showed a statistical improvement compared to a single injection of PRP or CS. The authors of the meta-analysis did note that the triple PRP injections were spaced out one

week apart from the previous dose. The authors also noted that the studies that looked at the triple PRP injections did not allow for three CS injections. There also appeared to be greater improvement with LR-PRP compared to LP-PRP. In summary, the authors concluded that PRP provides a statistically significant improvement in pain and stiffness measured by the WOMAC and VAS scores. The authors also noted that the benefits of PRP lasted longer than CS injections and that, if possible, three injections should be preferred to a single injection of PRP.

The strengths of this study include that at the time of publication, it was the first meta-analysis of PRP compared to CS. The authors also focused on standard outcome measurements, such as the WOMAC and VAS scores, to determine results. Additionally, the authors factored in the differences between each of the studies when doing their analysis. The limitations of the meta-analysis include the variation in length of time for which results were recorded in each study was not always consistent. There was also no standardization in the preparation of the PRP injections, which the authors note could play a significant role in efficacy of PRP. The authors of the meta-analysis declared no funding received for doing the analysis and denied any potential biases.

Discussion

The data presented in the studies evaluated shows a statistically significant benefit of platelet-rich plasma injections as compared to corticosteroid injections for pain reduction and functionality improvement. There are many factors to consider when choosing between injections for patients. The goals of both medications, however, are to reduce symptoms of osteoarthritis and return functionality to the joint suffering from degenerative changes.

Short-term treatment of osteoarthritis showed benefits from both PRP and corticosteroid injections. Elik et al. (2020) saw PRP produce an overall 55.9% reduction of symptoms on the

WOMAC scale, which measures three subcategories: pain; stiffness; and functionality. The study noted improvement in patients as early as one-month post-injection with benefit lasting out to 6 months. Sun et al. (2021) also noted a benefit with PRP injections in both WOMAC and VAS scoring. VAS scoring looks solely at pain and saw a mean reduction from 45.6 ± 13 in scores to 16.9 ± 13.4 at one month after injection. The WOMAC score was reduced from 29.9 ± 12.9 to 13.2 ± 9.0 at one month. These studies both suggest that PRP is a viable and reasonable treatment option for fast relief of symptoms related to OA. Of note, Sun et al. (2021) saw peak benefit of PRP at three months, with some lessening of benefit by six months. Elik et al. (2020) did not list any adverse effects, and Sun et al. (2021) reported five incidents of minor, unspecified adverse events. The five reported incidents all self-resolved without any treatment. This is an important consideration for PRP as it shows that it is a reasonably safe treatment option with minimal side effects.

Corticosteroid injections were also beneficial as a short-term treatment option. As noted in Zhong et al.'s meta-analysis (2020), steroid injections can help patients with symptom relief as early 1-2 weeks post-injection. The largest change, however, was noted to be around 3-4 weeks after injection with a 95% CI: -1.93 [-3.34, -0.52]. This benefit does not appear to last as long when compared to the PRP injections and by 8 weeks there was a reduction in reported benefit from corticosteroid IA injections. Similarly, the cohort study by Matzkin et al. (2017) showed a 34% improvement in WOMAC scores at three weeks and 37.6% at six weeks. However, the benefits then started to decline and by three months the benefit reduced back to 34.4%. An outlier to the data, the WOMAC score at six months post-injection saw another increase in symptom reduction of 40.2% (Matzkin et al., 2017). Of note, the VNS (Visual Numeric Score) that Matzkin et al. also recorded for the study did not show a statistically nor clinically

significant change in benefit at any point in their study out to six months. This conflicting data does agree that there is benefit short term with corticosteroid injections, but the benefit past three months is questionable.

To further assess the effectiveness of corticosteroids past three months, Conaghan et al. (2017) reviewed two formulations of corticosteroids, one extended release and one rapid release. These two formulations were compared to a placebo and data was measured over the course of 24 weeks. Overall, both formulations showed an improvement in the Average Daily Pain (ADP) scale when compared to the placebo. The benefits lasted eight weeks before symptoms began worsening again in both formulations. By 16 weeks, there was very little difference between the placebo and the two steroid injection groups, and the benefits continued to decline out to 24 weeks. Another study done by Nunes-Tamashiro et al. (2022) showed no statistical differences in VAS scores compared to a placebo saline injection at any point in the 52 weeks of evaluation. The WOMAC scores, however, did show improvement out to 52 weeks after injection. The baseline score was 5.29 ± 2.06 for the steroid group, with a change to 2.91 ± 2.73 at 52 weeks. The placebo group, however, also noted a benefit from 5.25 ± 1.97 to 2.62 ± 2.15 at 52 weeks. In both studies, there was improvement from baseline past three months and possibly up to 52 weeks. However, the benefit did start to decrease after three months and when compared to placebo, there was minimal clinical difference between the two scores.

Platelet-rich plasma appeared to have a longer period of benefit than corticosteroid specifically in regards to knee OA. Altamura et al. (2020) found a EQ-VAS improvement from baseline of 73.6 ± 11.9 to 80.6 ± 11.6 at two months ($p=0.004$), 82.2 ± 9.1 at six months ($p< 0.0005$), 81.0 ± 10.4 at 12 months, and 85.5 ± 8.6. In summary, there was steady improvement post-PRP injection at all time frames assessed with peak efficacy at 24 months. This study also

saw similar improvement with the IKDC scoring system as well as Tegner scores. Interestingly, Altamura et al. (2020) found that almost half of the patients (48.6%) were able to return to the same level of sport activity that they were capable of before having any osteoarthritic symptoms and in total, 76.6% of the patients were able to return to some sport activity, although not necessarily the same level of activity as prior to symptom onset. Ankle osteoarthritis, however, may have little to no benefit from PRP, according to Paget et al. (2021). The authors found no statistically significant improvement at any point in their study, which assessed from six weeks to 24 weeks. There were some significant limitations to this study, including lack of consistency in PRP concentration and lack of testing done on the PRP material used prior to injection. Additionally, the study had more participants in the placebo group to start with and the PRP lost two more participants during the study, which may decrease accuracy of results.

In summary, PRP appears to be an effective treatment option for osteoarthritis. There appears to be benefit lasting from one-month post-injection (Elik et al., 2020; Sun et al., 2021) out to possibly 52 weeks (Altamura et al,, 2020). Corticosteroids also showed improvement with symptoms early on as authors Matzkin et al. (2017) and Zhong et al. (2020) found improvement in symptoms within three months or less post-injection. Zhong et al. (2020) suggested that there was benefit as early as 1-2 weeks after injection with corticosteroids. In a direct comparison of the two treatments, Elksniņš-Finogejevs (2020) found that both PRP and corticosteroids can help reduce pain and improve functionality in OA patients. PRP did appear to be superior as seen with the one-year VAS score which changed from the baseline by -3.1 ± 2.0 as compared to the CS group which had a change of -0.8 ± 1.8 (p=0.0002). Corticosteroids showed quicker improvement with a change of -3.4 ± 1.2 at one week compared to the PRP change of -2.8 ± 2.3. Maximum functional benefit was seen for PRP at 15 weeks with a total change in IKDC score of

41.1 ± 13.6 and KSS of 33.7 ± 13.5. Maximum functional benefit for corticosteroids was noted at five weeks with a IKDC change of 30.2 ± 11.7 and KSS change of 29.4 ± 12.8. In short, PRP had better overall improvement in both pain and function with benefit lasting longer than CS. McLarnon and Heron's meta-analysis (2021) showed similar results with the most pronounced benefit in WOMAC and VAS scores at 6-9 months compared to corticosteroids.

Although this data suggests that PRP may have a more significant improvement, as well as a longer lasting improvement for OA symptoms and functionality, there are many variables that would need further research. There may be variation in efficacy depending on which joint is being injected. Additionally, there are many ways to formulate PRP and without standardization results can vary widely as noted in Paget et al.'s study (2020). The stage of OA may play a large role in benefit as well and further research would be needed to determine efficacy at each Kellgren-Lawrence stage of OA. All the studies for PRP that were listed showed either no adverse events or very few minor adverse events that resolved on their own. One study, Conaghan et al. (2018), reported adverse events that required treatment including an increase in non-joint related infections and one insufficiency fracture following corticosteroid injection. Despite needing further research, current data suggests that platelet-rich plasma can be a more efficacious and safe treatment for osteoarthritis by decreasing pain and improving functionality compared to corticosteroids.

Conclusion

PRP injections are more effective than corticosteroid therapy at relieving pain and improving function in patients with OA. There is some variation in methodology for PRP injections which may affect the outcome, such as the intra-articular approach, formulation, and frequency of injections. Corticosteroid injection dosing, frequency, and medications also varied

throughout the studies which may affect the degrees of pain relief and functional improvement patients experienced while being treated with corticosteroids.

With the noted variation in both methods, more research needs to be done in direct comparison of the two treatments. Additionally, PRP formulation and dose scheduling needs further research to evaluate optimum benefit. As noted in Paget et al.'s (2020) study, there was no significant benefit in ankle osteoarthritis from PRP which suggests response may be determined by which joint is being treated.

Application to Clinical Practice

Platelet-rich plasma injections are a viable option for treatment of osteoarthritis. The safety profile is better than that of the current mainstay treatment of intra-articular corticosteroid injection. As noted above, the variation in formulation could potentially change the effectiveness of the treatment for patients. Additionally, there may be some variation in benefit dependent on the specific joint being injected. Overall, PRP intra-articular injections effectively relieve pain and improve functionality. The PRP benefits are also noted to last longer than corticosteroid intra-articular injections and the peak benefit is noted to be greater which means patients may be able to reduce the number of injections they receive and still achieve better outcomes. The procedure can be completed in outpatient orthopedic clinics or family medicine clinics if properly equipped. Aside from preparation, there is no difference intra-articular approach between PRP and corticosteroids.

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